Highlights of the Year

Research

In 2015 Cold Spring Harbor Laboratory celebrated its 125th year. Today's CSHL is renowned for its research in Cancer, Neuroscience, Plant Biology, Quantitative Biology, and Genomics. Scientists at the Laboratory work together, frequently across disciplines, to solve biology's most challenging problems. This collaborative spirit and the scope of the faculty's research interests are suggested in this sample of a few of the past year's important findings.

Organoids to Aid Pancreatic Cancer Research

D. Tuveson

All cancer research relies on a steady supply of cells, both normal and cancerous, that can be grown in the laboratory. By comparing normal cells to cancer cells, scientists can identify changes that lead to disease. Yet both types of pancreatic cells have been difficult to culture in the laboratory. Another problem in studying pancreas cancer is the fact that many patients when diagnosed are already beyond the point at which surgery is useful, making it difficult or impossible in many cases to obtain tumor samples. To address this, CSHL's David Tuveson, in concert with the Dutch scientist Hans Clevers, has developed a method to grow pancreatic tissue directly from cells sampled from cancer patients. The cells form tiny spheres called organoids that are entirely made up of ductal cells, eliminating the surrounding cell types that often contaminate samples from the pancreas. They grow within a complex gel-like substance filled with growth-inducing factors and connecting fibers. Once they have grown to a sufficient size, the organoids can be transplanted into mice, where they recapitulate human pancreatic cancer. The Tuveson lab has used organoids to interrogate new therapeutic targets in pancreas cancer; David Spector's lab has used a similar method to study targets in breast cancer. The hope is that by testing drugs in these three-dimensional hollow spheres made of tumor cells and comparing them to a patient's normal cells—which can also be grown into organoids—we will be able to much better predict patient treatment outcomes in the clinic.

Biomarker for Treatment-Resistant Prostate Cancer

L. Trotman

In 2015 a new animal model for prostate cancer called RapidCaP emerged from Lloyd Trotman's lab. It is the only model in mouse in which the cancer metastasizes to the bone. This is precisely what happens in advanced metastatic prostate cancer. It is crucial to have such a model, because patient responses to hormone therapy vary widely, and it is still unclear why some types of prostate cancer seem to be resistant to the therapy. Those cases that resist therapy—a minority—are liable to become metastatic and are often lethal. Crucially, Trotman's model may help us determine which ones. His team has been using this system to trace the mechanisms underlying metastatic lesions. So far they have discovered that such lesions are very different from primary tumors in the prostate. Their work has shown that these metastases activate a pathway that involves the interleukin-6 (IL-6) protein, which activates the MYC oncogene that is expressed specifically in therapy-resistant metastatic prostate cancer cells. Using the IL-6 marker or associated proteins to predict which patients would benefit from hormone therapy would be a major advance. The hope is that translating the IL-6 discovery into clinics could help stratify patients into good responders and bad responders.

Brain Circuit Implicated in Schizophrenia

The prefrontal cortex (PFC) plays an important role in cognitive functions such as attention, memory, and decision-making. Faulty wiring between the PFC and other brain areas is thought to

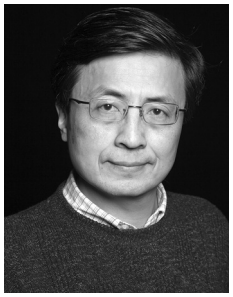

B. Li

give rise to a variety of cognitive disorders. Disruptions to one particular brain circuit—between the PFC and another part of the brain called the thalamus—have been associated with schizophrenia, but the mechanistic details are unknown. Bo Li and colleagues have now discovered an inhibitory connection between these brain areas in mice that can control the timing of information flow into the PFC. This insight may help explain what goes wrong in schizophrenia and indicate a path to new treatments. The team used optogenetic stimulation, a technique in which neurons expressing a light-sensitive protein are controlled with pulses of light, to observe a process called feed-forward inhibition, a mechanism in which one neuron excites a neighboring or "downstream" neuron but also recruits a third neuron to inhibit the downstream target after some delay. They will now use a genetic mouse model of schizophrenia to determine if there are any noticeable changes in the observed feed-forward inhibition in the thalamus–PFC pathway; these in turn might suggest novel targets for next-generation schizophrenia therapeutics.

Cholinergic Warning System

In experiments with mice, Adam Kepecs and colleagues discovered a set of dedicated neurons in the basal forebrain that broadcast messages throughout the cerebral cortex, rapidly informing multiple distributed subregions of any surprising rewards or punishments. The neurons are cholinergic—they send signals in the form of the neurotransmitter acetylcholine. Such neurons are thought to play an important role in arousal, attention, and learning, yet their precise role in behavior has remained mysterious, in part because of the technical difficulty in recording from them in vivo. Degeneration and loss of cholinergic neurons in the basal forebrain have been implicated in Alzheimer's disease, age-related cognitive decline, and other cognitive disorders and dementias. Kepecs' team showed how central cholinergic neurons function, using optogenetic methods as mice performed behavioral tasks that involved rewards or unexpected mild punishments. To explain their responses the team constructed a computational model that revealed that the modulation of signal strength was proportional to how unexpected or surprising the mice found the reward or punishment. According to the model, if the mice were confident their response was correct, the reward generated a weak signal. But if they were unsure, the reward came as more of a surprise and generated a stronger cholinergic signal. Kepecs suggests that cholinergic broadcasts to the cortex would be useful in boosting plasticity, allowing flexibility in neuronal connections that makes learning possible. Whether a surprise is positive or negative, the fact that it is unexpected, and the degree to which it is, would be an obvious advantage to the individual.


A. Kepecs


J. Huang

How a Brain Circuit Controls Fear

It is hard to imagine that an intangible emotion like fear is encoded within neuronal circuits, but Bo Li and colleagues have found that fear is stored within a distinct region of the brain. In recent years, they have discovered that fear learning and memory are orchestrated by neurons in the central amygdala. Now, Li, along with CSHL collaborators Josh Huang and Linda Van Aelst, took on the question of what controls the central amygdala. They focused on a cluster of neurons that form the PVT, or paraventricular nucleus of the thalamus. This region is extremely sensitive to stress, acting as a sensor for both physical and psychological tension. The team found that the PVT is specifically activated as animals learn to fear or as they recall fear memories. They were able to see that neurons from the PVT extend deep into the central amygdala. Disrupting the connection significantly impaired fear learning. Perhaps most important, in looking for molecular mechanisms that connect the two structures, the team


L. Van Aelst

used data from people with post-traumatic stress disorder to discover that the well-known neural growth factor BDNF is the chemical messenger that allows the PVT to exert control over the central amygdala. This provides a promising target for the future treatment of anxiety disorders.

Mastering CRISPR to Reveal Cancer Targets

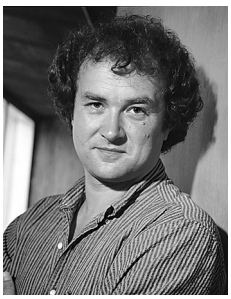
C. Vakoc

Since assembly of the full human genome sequence in the early 2000s, scientists have been amassing databases that document or predict how specific stretches of DNA letters in the genome encode specific segments of proteins, called domains. Among the domains of greatest interest to drug developers are those that form pocket-like features on the surface of proteins that other molecules can fit into, as keys fit into locks. Drugs are keys that fit into binding-pocket locks, sometimes for the purpose of blocking access to the lock, and other times to initiate a cascade of signaling inside the cell. Watson School doctoral student Junwei Shi spent a year in Chris Vakoc's lab mastering the new genome editing method called CRISPR-Cas9, which has taken the world of biology by storm. He and Vakoc used the technique to mimic the effect of drugs binding to protein targets on leukemia cells—thousands of different targets in a single experiment. This multiplexing approach yielded exciting results, successfully identifying six previously known targets and revealing 19 previously undiscovered ones in just one leukemia screen. Each one is a binding pocket that if blocked by a drug would result in cell death—in other words, a target that the cancer cell depends on to thrive. It was a proof of principle. The method can be used by academic labs and by drug developers to generate catalogs of the most effective druggable targets for cancer cells, across different cancer types and subtypes.

Our Probabilistic Approach to Numbers

A. Churchland

Humans, including preverbal babies and adults in indigenous cultures with no formal mathematical education, are capable of estimating numbers of objects. Yet although areas of the brain have been identified that respond to specific numbers, it has been unclear how numbers are represented. Scientists have generally assumed that the brain represents numbers of objects as single, whole values, or "scalars." However, estimates of many other features of the environment—such as object depth, height, and location—have been shown to be "probabilistic," represented as a range of values. In 2015 Anne Churchland and colleagues reported results of an experiment combining auditory and visual cues to test whether people have a scalar or probabilistic sense of numbers. They determined that even a distinct number of objects in the world may be represented in the brain not as a single value but as a range of possible values. Subjects could perform an audiovisual task involving a numerical determination with any of three strategies. Some employed only the most reliable piece of information; others combined auditory and visual information to arrive at an estimate; still others randomly picked one piece of information on which to base their number estimate. These results have important implications for how we learn and understand our world. Representing numbers as a range of possible values allows people to utilize multiple streams of information, leading to improved decisions.



N. Tonks

Reversibility of Rett Syndrome Symptoms

S. Shea

Another example of collaborative science at CSHL is newly published work that is the fruit of discussions among members of the laboratory groups of Nicholas Tonks, Stephen Shea, and Josh Huang. The idea behind Tonks and colleagues' 2015 report of an experimental drug treatment to reverse symptoms of Rett syndrome, an autism spectrum disorder, can be traced to a discussion among investigators working in the three

labs. They realized there might be some benefit in applying to a mouse model of Rett syndrome some of the work that's been done in the Tonks lab in developing small-molecule drugs that inhibit an enzyme called PTP1B, which Tonks discovered 25 years ago. Realizing that metabolic regulation appears to be abnormal in Rett syndrome—a largely unappreciated fact—Navasona Krishnan, a Research Associate who works with Tonks, proposed using inhibitors of PTP1B to see if they might address any of the range of symptoms seen in the disease. He first demonstrated that PTP1B levels were abnormally elevated in the model mice. This was an encouraging sign that inhibitors of PTP1B might have a beneficial effect. More exhaustive experiments with several candidate small-molecule inhibitors demonstrated that they can significantly extend life span in male mice that model Rett syndrome and can ameliorate several behavioral symptoms of the disorder in model female mice. This was tantalizing evidence that Rett symptoms can actually be reversed and supports the concept that the disorder may be amenable to treatment with small molecule drugs—an objective the team continues to pursue vigorously.

Fine-Tuning Plant Growth to Optimize Fruit Size

A wonderful example of basic science having an important societal impact is work from Zach Lippman's laboratory. His discoveries in recent years have identified a number of things that can be done by growers to increase fruit yield. This year Lippman and colleagues identified a set of genes that control stem cell production in tomato. Mutations in these genes explain the origin of mammoth beefsteak tomatoes. More important, the research suggests how breeders can fine-tune fruit size in potentially any fruit-bearing crop, a significant advance for agriculture. The secret of the beefsteak tomato, the team showed, has to do with the number of stem cells in the plant's growing tip, called the meristem. They traced an abnormal proliferation of stem cells to a naturally occurring mutation that arose hundreds of years ago in a gene called *CLAVATA3*. Selection for this rare mutant by plant cultivators is the reason we have beefsteak tomatoes today. Lippman's team examined never-before-studied mutant tomato plants, three of which contained faulty genes encoding enzymes that add sugar molecules to proteins. Their experiments revealed that the enzymes, called arabinosyltransfersases (ATs), add sugar molecules called arabinoses to CLAVATA3. By adjusting the number of sugars on CLAVATA proteins, and through other mutations affecting components of the pathway, Lippman and colleagues show it is possible to fine-tune growth in ways that could allow breeders to customize fruit size.

Z. Lippman

Overcoming Bad Karma

Epigenetics pioneer Rob Martienssen, whose discoveries confirm and extend the observations and predictions of CSHL Nobel laureate Barbara McClintock, this year solved a 30-year-old mystery that had cost growers of the oil palm tree hundreds of millions of dollars in ruined crops. In the 1980s, a new method of generating plantations brimming with clones of the highest-yielding specimens of the oil palm plant met with unanticipated disaster. Corporate investors were astonished to observe that the finest hybrids, cloned in culture dishes, often grew into barren adults bearing desiccated, worthless fruits. These plants displayed a mutant form that scientists called "mantled." Martienssen's work, aimed at more completely understanding how epigenetic mechanisms influence and even control plant development and evolution, traced the problem to a transposable element lodged within the oil palm gene called *MANTLED*. This "jumping gene" is an example of the myriad genomic invaders that lay (mostly) dormant within and between genes in all forms of life. This particular invader, or one very similar to it, was first spotted in rice plants and had been named *karma*. Martienssen and colleagues discovered that in mantled plants, a methyl mark present in healthy plants was missing at a location in *karma* called a splice site.

R. Martienssen

When the splice site is unmethylated, the RNA message copied from the gene encodes a mutant protein that gives rise to plants with worthless fruit. A simple epigenetic test will readily identify bad *karma* and thus enable growers to cull damaged clones at the plantlet stage. It will promote the propagation of healthy high-value hybrid clones and thus reduce the economic pressure on growers large and small to devote additional tropical rainforest territory to oil palm cultivation.

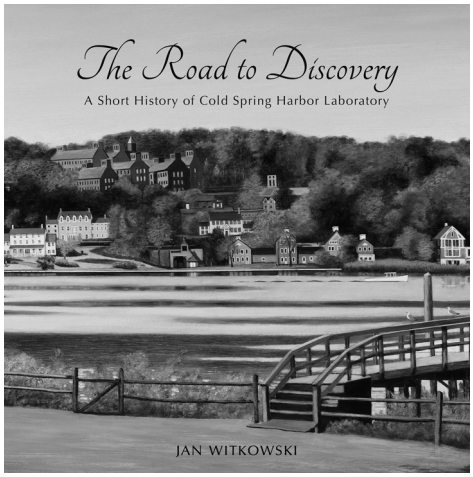
1890–2015: The Laboratory's 125th Anniversary

July 7, 1890 marked the first day of the first course ever given at The Brooklyn Institute's Laboratory of Biological Research at Cold Spring Harbor. The first scientists to come to learn and research at Cold Spring Harbor paid $24 in tuition and were encouraged to bring their own microscopes. We celebrated the 125th anniversary of this day—the start of what is today CSHL—continuously throughout the year with a diverse set of events designed for our own campus community, the broader scientific community, and the public.

More than 600 people visited the Bungtown Road campus on June 6 for a public celebration of the 125th Anniversary. The Open House featured stations representing all research and education divisions in "expo-style" format that encouraged visitors to interact with our faculty, students, and staff.

Especially popular were campus mini-tours running throughout the day, which took more than 300 guests through campus and were led by Ph.D. students and postdoctoral researchers. Kids and adults alike crammed booths where DNA Learning Center teachers led hands-on biology demonstrations, featuring DNA extraction and mutant fruit flies. All of CSHL's research areas were represented by science researchers with hands-on and interactive stations in the just-completed Nicholls Biondi Hall. A special treat for the event was a painting of the CSHL campus landscape commissioned privately by Dill Ayres. It was on display with its creator, famed local painter William Jonas, who spoke to visitors about the painting. We were also pleased to host the Cold Spring Harbor High School Research Symposium as part of the day's events, featuring CSHL Professor and Lustgarten Foundation Director of Research Dr. David Tuveson, who delivered the keynote, *Avoid Boring Problems*.

Open House



The Road to Discovery

Raft Race

Many thanks to all of the faculty, students, and staff who made the Open House such a special day for so many in our community. We also appreciate the year-long efforts of many of our graduate students and postdoctoral fellows who serve as ambassadors to the community, guiding our public tours on weekends and for visiting civic, student, and other organizations. Over the year, more than 1500 visitors were treated to these professionally guided tours on the history, contemporary science, and education programs of CSHL.

A special anniversary public lecture series also brought scientific luminaries to the Lab throughout the year. (See the calendar of these events listed at the end of this section.) To commemorate and share our anniversary more widely through print and digital channels, the Public Affairs Department developed an interactive digital timeline of CSHL's historic contributions to society (discoveries.cshl.edu) and the CSHL Press published *The Road to Discovery: A Short History of Cold Spring Harbor Laboratory* by our own Banbury Center Executive Director Jan Witkowski.

I also hope that our faculty, students, and staff enjoyed the many celebratory events on campus, designed and executed by a volunteer committee. Congratulations, too, to all of the winners of competitions that included, a raft race, karaoke, CSHL trivia, and a scavenger hunt!

CSHL-North Shore LIJ Health System (Northwell Health) Affiliation

On April 5, CSHL and Northwell Health (previously the North Shore-LIJ Health System) announced a strategic affiliation to align the Lab's world-class cancer research with Northwell's growing network of clinical services encompassing more than 16,000 new cancer cases annually across the New York metropolitan area.

The CSHL-Northwell affiliation will benefit from the investment of more than $120 million to accelerate cancer research, diagnosis, and treatment. Funds will be used to advance cancer therapeutics research, develop a new clinical cancer research unit at the North Shore-LIJ Cancer Institute's headquarters in Lake Success, New York to support early-phase clinical studies of new cancer therapies and recruit and train more clinician–scientists in oncology.

Bruce Stillman and Michael Dowling at the signing of the CSHL-Northwell Health affiliation.

It is a transformative affiliation for both institutions, bringing the cutting-edge basic discovery science and translational cancer research at CSHL to one of the largest cancer treatment centers in the United States. The unique integration of research scientists, clinical translational researchers, and cancer clinicians promises to speed the advance of novel cancer diagnostics and therapeutics to patients in the region.

The affiliation will recruit cancer researchers and clinicians to the region. As part of the collaboration, clinician–scientists will be trained to perform preclinical cancer research and conduct early-stage human clinical trials. Positive findings from this partnership in research and therapeutics will form the basis for advanced-phase clinical trials to be conducted at both Northwell facilities and collaborating outside medical centers. Patients cared for at Northwell facilities will benefit from increased access to these innovative clinical studies.

Under the terms of the strategic affiliation, Northwell and CSHL will continue as independent organizations governed by their respective Boards of Trustees. A committee with responsibility for oversight, staffing, and implementation of the affiliation includes three representatives of CSHL: President and CEO Dr. Bruce Stillman, Director of Research Dr. David L. Spector, and Cancer Center Deputy Director Dr. David Tuveson; and three representatives of North Shore-LIJ: Physician-in-Chief and Dean of the Hofstra-Northwell School of Medical School Dr. Lawrence G. Smith, Feinstein Institute for Medical Research President and CEO Dr. Kevin J. Tracey, and Dr. Thomas McGinn, Chair of Medicine.

Economic Impact of the Lab

The Laboratory commissioned a study by the private consulting firm Appleseed of its direct and indirect impact on the Long Island and New York State economies. Based on 2013 data, *Shaping Long Island's Bioeconomy: The Economic Impact of CSHL* highlighted the institution as an enterprise directly employing 1100, indirectly accounting for more than 500 additional jobs, and annually bringing more than $140 million in revenue to Long Island from Federal grants, private philanthropy, an array of scientific educational programs, and commercialization of technologies. The private, not-for-profit Laboratory's research revenue in 2013 totaled $104.3 million, an increase of 65% since 2003.


Newsday
LI BUSINESS
DOW JONES
▲46.34 to 18,070.40
CRUDE OIL
▼$0.22 to $58.93
S&P RISES TO A NEAR RECORD
Lab boosting economy
Report: Research at Cold Spring translates to jobs
BY JAMES T. MADORE
COLD SPRING HARBOR LABORATORY
Cold Spring Harbor Lab has helped to start eight businesses since 2011, and licensing of its drug discoveries brought the lab about $50 million last year, according to a new assessment of the lab.

Newsday article about the Lab's economic impact

The study found that CSHL "to an extent few other institutions can match" is equipped to address the demands of what the National Research Council (NRC) calls "the new biology." This involves integrating insights across normally "siloed" disciplines, ranging from information and computer technologies to physics, and putting them to work to solve pressing problems, from new approaches to treating cancer and disabling brain disorders to developing insights that result in increased food production and the generation of clean, low-cost biofuels.

Furthermore, the study concluded that the impact of the Lab is multiplied through its collaborations with other New York institutions and companies, including Stony Brook University and Brookhaven National Laboratory in neuroscience and biofuels, and with health-care institutions like Northwell Health. Partnerships with biotechnology and pharmaceutical companies such as GSK, Pfizer, Boehringer Ingelheim, Dart Neurosciences, Isis Pharmaceuticals, Merck, and Syngenta enable the Lab to speed the process of turning research developments into tangible benefits to society.

Business Development & Technology Transfer

The Business Development & Technology Transfer program supports the Lab's scientists with industry and investor engagements in seeing CSHL discoveries reach the public. In 2015 we added several new technology projects and 18 new patent filings bringing the portfolio under management to 142 technologies covered by more than 500 active patent cases. Eleven new industry-sponsored research or collaboration agreements were signed and 21 new license and option agreements were signed, including:

- the **GSK DPAc** research collaboration initiated to identify new therapies for metabolic diseases
- **Hairpin LLC**, launched as our licensing agent for the shRNA technology and a platform for distribution of enabling research technologies developed at CSHL
- research collaborations with **Pfizer, BI, and Syros** in Chris Vakoc's CRISPR innovations
- the exercising of **ASOthera Pharmaceuticals**' option to a full license with equity and transitioned to a real company, well financed with excellent management
- **Marvel Genomics,** our newest spin-out, off to a good start with an energetic start-up CEO, an experienced executive in the CSHL board seat, and two corporate partnerships in discussion

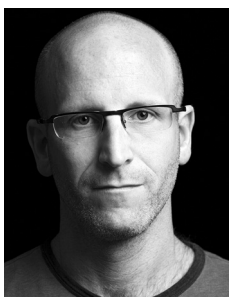
Research Faculty

Awards

Evelyn Witkin, Ph.D., who worked as a geneticist here in the formative years of molecular biology, was honored at age 94 with a Lasker Award for achievement in Basic Science. Evelyn made her mark in biology by identifying mechanisms of DNA repair and recombination through experiments on bacteria. (See a detailed account of her career at the CSHL Library & Archives website.)

E. Witkin

She earned her Ph.D. in 1947 with Theodosius Dobzhansky at Columbia University, but she was directed by Dobzhansky to study with then–CSHL Director Milislav Demerec where her interests turned to bacterial genetics, and she spent the summer of 1944 at Cold Spring Harbor, where she isolated a radiation-resistant mutant of *Escherichia coli*. Evelyn continued her studies on the shores of Cold Spring Harbor as part of the Carnegie Institution Department of Genetics until 1955. Subsequently she took a position at the State University of New York's Downstate Medical Center in Brooklyn, and in 1971 became a professor at Rutgers University. She was named Barbara McClintock Professor of Genetics in 1979 and was appointed in the Waksman Institute at Rutgers in 1983. Evelyn retired in 1991.



A. Zador

Professor Anthony Zador was recognized by the editors of the prestigious journal *Foreign Policy* in the category of "Innovators," for "testing the boundaries of the brain, our most powerful organ," according to the journal. Others receiving "Top 100" honors in recent years have spanned the gamut of achievement, from Pope Francis to Angela Merkel to Elon Musk. Tony was recognized for his work on developing a wiring diagram of the mouse brain at the resolution of individual neurons.

M. Timmermans

Professor Marja Timmermans, a distinguished plant geneticist who has spent most of her career at the Lab, began a new phase of her work in April, as an Alexander von Humboldt Professor at Germany's Tübingen University. Germany's most prestigious international research prize was presented by that nation's Research Minister, Professor Johanna Wanka, and President of the Humboldt Foundation, Professor Helmut Schwarz. Marja has made several internationally acclaimed discoveries. She has explained key mechanisms behind leaf development in plants and, most recently,

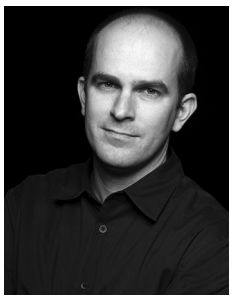
demonstrated the mobility of small RNA molecules and how this establishes leaf polarity—the process through which leaves flatten and develop distinct top and bottom surfaces optimized for photosynthesis. She began her career at CSHL in 1998 and was named assistant professor in 2001 and professor in 2009.

Two neuroscientists were awarded prestigious NARSAD Independent Investigator grant by the New York City–based Brain and Behavior Research Foundation (BBRF). Adam Kepecs and Bo Li, both associate professors, were among 40 mid-career scientists from 30 institutions in 16 countries selected for the honor this year. The awardees were selected by the Foundation's Scientific Council, comprised of 150 leading experts across disciplines in brain and behavior research, including two Nobel Prize winners and four former directors of the National Institute of Mental Health.

A. Kepecs

Adam will take advantage of new light-based genetic tools to monitor and manipulate the activity of cells that release the neurotransmitter serotonin in mice. Serotonin levels are modulated by drugs to treat depression, anxiety, panic disorder, chronic pain, and other psychiatric conditions, but when serotonin neurons are activated during behavior remains unclear. His experiments are designed to clarify the behavioral roles of these central serotonergic neurons.

Bo aims to elucidate the mechanisms that cause abnormal fear processing in anxiety disorders such as post-traumatic stress disorder. He will use his grant to investigate brain circuits in the anterior insular cortex and the amygdala, brain regions that are activated during the experience of fear and hyperactive in people with anxiety disorders.



C. Vakoc

The American Association for Cancer Research (AACR) honored Assistant Professor Christopher R. Vakoc, M.D., Ph.D., with the 35th annual AACR Outstanding Achievement in Cancer Research Award. Since 1979, the AACR Award for Outstanding Achievement in Cancer Research has been awarded to an investigator younger than 40 years of age to recognize his or her meritorious achievements within the field of cancer research.

Chris was recognized for his groundbreaking discoveries in the areas of epigenetics and cancer biology. His research on the basic molecular mechanisms that control leukemias have revealed an essential connection between epigenetic regulation and oncogenesis. This work has led to the development of potential new therapeutic approaches—including a drug called a bromodomain inhibitor—currently being evaluated in early-stage clinical trials.

M. Schatz

Associate Professor Michael Schatz received a 2015 Alfred P. Sloan Foundation Research Fellowship. Mike was one of 126 outstanding early-career scientists from the United States and Canada recognized by the Foundation this year. Past honorees include the famous physicist Richard Feynman and 42 others who went on to win the Nobel Prize.

Mike is a quantitative biologist and a faculty member of CSHL's Simons Center for Quantitative Biology. From the very start of his career he has been recognized as an innovator in cloud computing and "big data." At CSHL, Mike has applied his quantitative insights to diverse problems, ranging from methods of assembling plant and animal genomes from raw DNA sequencing data to the analysis of large data sets generated in studies of people with diseases such as cancer and autism.

A. Gann

Dean of the Watson School of Biological Sciences Alexander Gann was awarded a 2015 Guggenheim Fellowship in science writing. Alex will use the award to write a book about the hunt for the so-called homeotic (or Hox) genes—the genes that control how the bodies of all animals are shaped. "Mutants in these genes were first identified, in the

fruit fly *Drosophila melanogaster*, 100 years ago," Gann says. "They were striking for their gothic, fairytale-like appearance: legs growing out of heads in place of antennae, or an extra sets of wings growing out of the body." The genes were isolated in 1982 and found to be conserved—shared across evolutionary time—in all animals. This result heralded in the era of molecular developmental biology and the now-flourishing field of Evo-devo. Alex intends to chronicle both the fascinating science and the rich menagerie of characters behind the discovery.

Guggenheim Fellowships are awarded to individuals who have established themselves as exceptional scholars and artists. James Watson, chancellor emeritus, received two Guggenheim Fellowships, his first, in 1965, for the writing of the original edition of *The Double Helix*. Former CSHL scientists honored as Guggenheim scholars include Barbara McClintock (1933), Salvador Luria (1942), Renato Dulbecco (1957), and Rich Roberts (1978), as well as the current head of Simons Center for Quantitative Biology, Adam Siepel.

J. Sheltzer

Newly appointed CSHL Fellow Jason Sheltzer received the 2015 Early Independence Award from the National Institutes of Health (NIH) High Risk, High Reward Research Program. With a Ph.D. in Biology from MIT, Jason joined CSHL in August to pursue cancer research. He was also named one of *Forbes* magazine's "30 under 30 in Science" earlier in the year. Jason is studying genes that may make a difference between tumors that are benign and those that are cancerous and likely to spread to other parts of the body, a process called metastasis. "In order to uncover new genes that play a role in cancer progression and to increase our understanding of the molecular differences between fatal and nonfatal tumors, we are analyzing data from cancer patient survival studies," explains Jason. He will use the latest genome-editing technology, called CRISPR, to establish the molecular links between these genes and cancer prognosis.

Luis A. Mejia, Ph.D., a postdoctoral investigator, was named a 2015 Arnold O. Beckman Postdoctoral Fellow. Mejia works in the laboratory of Bo Li and came to CSHL following doctoral training at Harvard University, where he was awarded an NIH NRSA predoctoral fellowship for his research in neuroscience. His project is of fundamental importance to understanding behavioral flexibility and has the potential to yield significant insights into the basis of human neuropsychiatric disorders. Mejia aims to understand how neural circuits encode behavioral flexibility and how changes in neural activity can give rise to maladaptive, abnormally repetitive behaviors. Such behaviors are seen in illnesses such as obsessive–compulsive disorder, autism spectrum disorder, Tourette's syndrome, attention-deficit hyperactivity disorder, and anxiety disorders. Mejia is establishing a mouse model of obsessive behavior that will enable him to evaluate the role of specific neuronal populations in these behaviors. He will focus on the striatum, a part of the brain important for behavioral flexibility.

Ian Peikon is the fourth CSHL graduate student to have won the prestigious (2015) Harold M. Weintraub Graduate Student Award. In April, Peikon graduated from the Watson School, where his studies focused on developing innovative and affordable methods to map the connections between neurons in the brain. A Long Island native who went to Bethpage High School, Peikon came to CSHL in 2009 with a BSE in Biomedical Engineering from Duke University.

Ian Peikon at the WSBS Graduation

Promotions and New Hires

Congratulations to the faculty who were promoted to Associate Professor: Florin Albeanu, Gurinder Atwal,

Alexander Krasnitz, Stephen Shea, and Christopher Vakoc. Camila dos Santos was named Assistant Professor.

The Laboratory also welcomed CSHL Fellow Jason Sheltzer. Charles S. Ryan joined as Vice President, General Counsel.

Education Programs

Banbury Conference Center

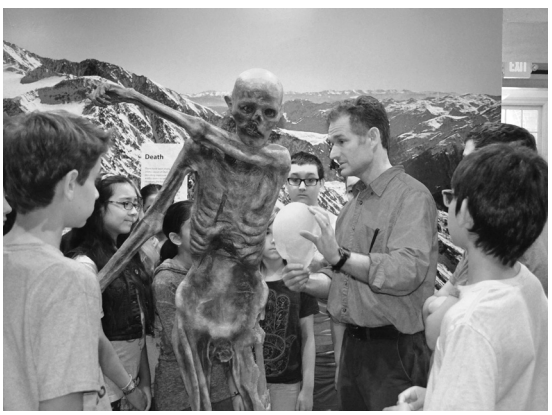
The Laboratory's think tank for biology and science-and-society issues attracted more than 600 participants this year. One highlight occurred in March, when those attending the "Exercise Science and Health" meeting attempted a critical review of the data and examined how far they can be trusted. As is often the case, it was difficult to get members of different fields with different practices to reach a consensus.

"HIV-1 and How to Kill a Killer" was the first meeting on HIV and AIDS to be held at Banbury since the early 1990s. Five participants in those early meetings were here in 2015. They and other attendees examined the vexed issue of where the virus hides in "cured" patients until it reappears years later. The meeting on "Therapeutic Use of Ketamine for Treating Severe Depression: Risks and Potential" was a follow-up to a meeting held in 2013 on the biology and pharmacology of an anesthetic drug being used with notable success in depression that does not respond to other treatments and as a suicide preventive. This year's meeting dealt with the question: Why, if ketamine is so effective in treating severe depression, is it not widely used? The answers involve complicated social, economic, and regulatory issues.

DNA Learning Center

In 2015 the DNALC served 20,570 students who attended field trips at facilities in Cold Spring Harbor as well as DNALC West and the Harlem DNA Lab. An additional 8908 students completed labs in their own schools, led by DNALC staff, whereas 1348 students attended week-long summer camps. The Center's popular Urban Barcode Project had a successful fourth year, with students presenting research posters and giving oral presentations at the American Museum of Natural History. Student teams supported by teachers from 20 schools in Nassau, Suffolk, and Queens counties presented project results at the inaugural Barcode Long Island symposium in June.

This year, the DNALC concluded negotiations to develop a DNA Learning Center Asia in Suzhou Industrial Park (SIP), near Shanghai, China. DNALC Asia has been registered as an "internal" Chinese NGO, sponsored by CSH Asia Conferences. It is being developed on a 270,000-square-foot site, and its first set of teaching labs will have twice the capacity of the Dolan DNALC facility in Cold Spring Harbor Village.



Ötzi the Iceman at the DNALC

The Dolan DNALC facility is now the home of a precise life-size reproduction of "Ötzi the Iceman," the mummified remains of a European male who lived about 5300 years ago. The unique replica provides the entry point for exploration of human origins, a longtime interest of the center. The exhibit is designed to complement experiments pioneered by DNALC, in which students use their own DNA as an entrée to the study of the human family and its dispersion across the planet.

Ohio high school senior Ryan Chester was awarded the first-ever Breakthrough Junior Challenge prize during a live broadcast hosted by Seth MacFarlane on the National Geographic Channel. The prize included a

state-of-the-art science and mathematics laboratory designed by the DNALC. Ryan's high school science lab was last renovated during the 1950s. The new lab will bring the school's classroom to 21st-century standards with a design based on the DNALC's highly successful open, collaborative laboratory concept.

Breakthrough Prize Ceremony: Priscilla Chan, Sal Khan, and winner Ryan Chester

Cold Spring Harbor Laboratory Press

The Press publishes eight journals, has 200 books in print and electronic form, and two web services. In 2015, a new journal joined the list. Subtitled "a journal of precision medicine" *Cold Spring Harbor Molecular Case Studies* illuminates the traditional medical case report with advanced laboratory investigations such as genome sequencing.

Confidence in this new publication is sustained by the success and reputation of the other Press journals. Online, the Press journals had a record download of more than 13.4 million full-text articles.

The year saw increasing adoption of bioRxiv, the online distribution service for preprints of research papers in the life sciences, founded in 2013. It permits scientists to make their work immediately available to the research community and receive feedback on draft manuscripts before submitting them to journals. The monthly rate of manuscript submission doubled between May and December and represented more than 1500 institutions in 40 countries. Launched with seed funding from the Laboratory, bioRxiv has since received critical support from The Lourie Foundation. Its emergence demonstrates that the Laboratory is continuing to pioneer new ways of advancing science by sharing results and ideas.

bioRxiv beta

THE PREPRINT SERVER FOR BIOLOGY

The bioRxiv logo

Watson School of Biological Sciences

In 2015 the Watson School graduated its 12th class. Students continued to graduate considerably faster than students in comparable Ph.D.-granting institutions and demonstrated an ability to secure excellent jobs. Twenty-one graduates have secured tenure track faculty positions. Seven have already been promoted to Associate Professor.

At the graduation ceremony, 12 students were awarded Ph.D. degrees, bringing the total since the school's inception to 83. During the year, scientific papers published by students of the school appeared in major journals, bringing the cumulative total to more than 300.

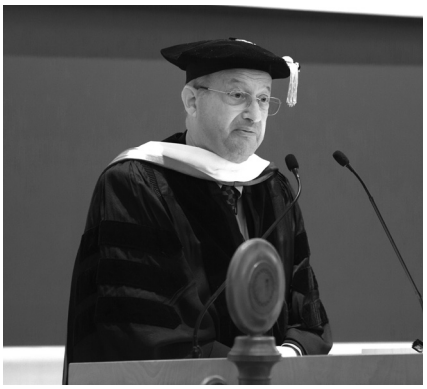
At the ceremony, Honorary Degrees were presented to Charlie Rose, Lord David Sainsbury, and Dr. Hanna Gray, as part of the celebration of the 125th anniversary of CSHL.

A leader in education and an advocate for scientific research, Hanna Holborn Gray, Ph.D. served as president of the University of Chicago from 1978 to 1993 and was the first female president of a major university in the United States. Lord David Sainsbury was Minister for Science and Innovation in the United Kingdom from 1998 and 2006. He established the Gatsby Charitable Foundation in 1967 with a particular emphasis on plant science and neuroscience. Journalist Charlie Rose was honored as a leader in public engagement, insight, and inquiry into contemporary topics of science and society.

In August, the WSBS matriculated seven new students, selected from among 310 applicants and representing the United States, Lithuania, Russia, the United Kingdom, and Vietnam. Other new graduate students entered as visitors from other institutions, including seven from Long

WSBS Honorary Degree recipient
Charlie Rose

WSBS Honorary Degree recipient
Dr. Hanna Gray



WSBS Honorary Degree recipient
Lord David Sainsbury

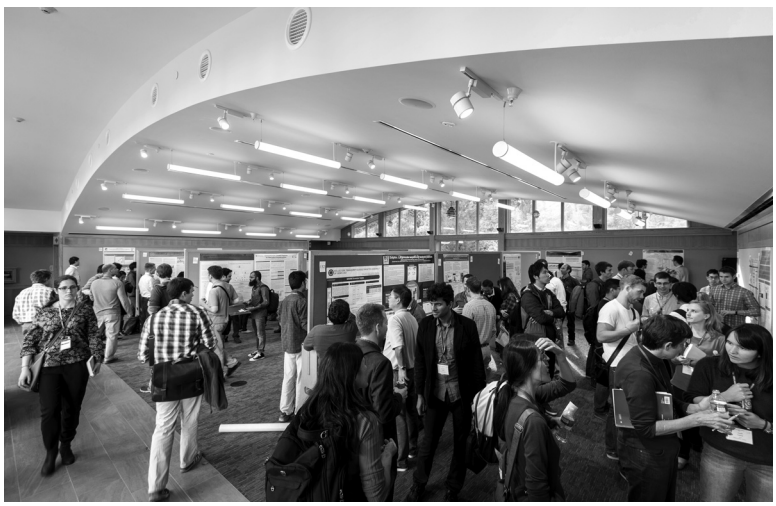
Island's Stony Brook University; other current visitors hail from institutions including Cornell University and the National Centre for Biological Sciences, India.

Meetings & Courses Program

In 2015, scientific meetings attracted almost 7600 participants to the main campus. When combined with participants in the China meetings, the program drew about 10,500 scientists in all. The year saw the continuation of many successful annual and biennial meetings, as well as the introduction of several new meetings, focusing on Immunology, Probabilistic Modeling in Genomics, and Genome Engineering. The latter meeting was a 2015 highlight, featuring the CRISPR genome editing technique, attracting more than 400 participants from around the globe.

In June, Cold Spring Harbor Asia Conferences hosted a special meeting in Suzhou, bringing together stakeholders in many of the national brain projects recently initiated around the world over.

More than 750 instructors, lecturers, and assistants came to teach at CSHL from universities, medical schools, research institutes, and companies around the world. During the year, about 700 trainees—who included advanced graduate students, postdocs, and faculty—attended courses lasting from one to three weeks.



Posters inside Nicholls Biondi Hall

In 2015 renewal was secured for course funding from the Howard Hughes Medical Institute, a longtime benefactor. New major multiyear grants were received from the Helmsley Charitable Trust and the National Institute of General Medical Sciences.

Infrastructure

The Laboratory completed two major construction projects during the year: a 10,000 square foot extension was added to the Woodbury Genome Center to house a new Preclinical Experimental Therapeutics Facility (PETx), and the Nicholls Biondi Hall was erected as a venue for scientific

New PETx wing of the Genome Center

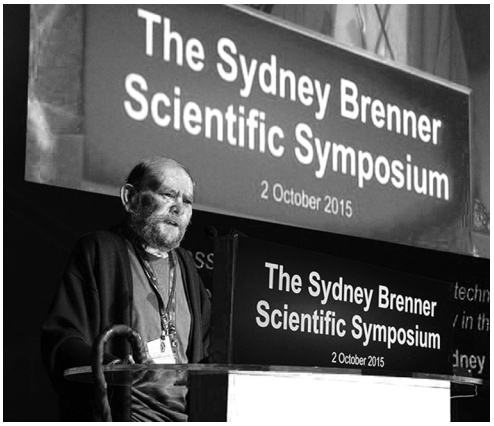
Nicholls Biondi Hall

poster sessions of the Meetings & Courses Program. With these two major projects completed, the Laboratory turned to a number of smaller projects to renovate and upgrade facilities and mechanical systems.

Library

The CSHL Library and Archives continued its commitment to exploring and preserving the history of molecular biology while also looking to the future to improve scientific communication to students, scientific investigators, and the public. An example of this outreach is the Cold Spring Harbor High School Eugenics Presentation, given again this year. Over the past four years, more than 100 high school seniors have come to CSHL for a tour, presentation, and discussion of eugenics as part of the local public school's History of Science class.

"A Heroic Voyage: Sydney Brenner's Life in Science" symposium and exhibition in October in Singapore was organized by Mila Pollock and A*Star, the Singapore Agency for Science, Technology, and Research. This tribute celebrated the Nobel Laureate, emphasizing his many scientific accomplishments and his leading role in the development of biomedical research in Singapore. The exhibit was curated by the CSHL Library and Archives, featuring photographs and memorabilia from our Brenner collection. We are grateful for Brenner's donation of his scientific papers to the CSHL Archives and for the Sydney Brenner Research Scholarship in the History of Molecular Biology, Genetics, and Biotechnology. The 2014–2105 scholarship recipient was Erika Langer, a doctoral candidate at the University of California, San Francisco, studying the early years of the CSHL yeast group.



The Sydney Brenner Scientific Symposium

"The Evolution of Sequencing Technology: A Half-Century of Progress" was organized by Mark Adams, Nigel Brown, Mila Pollock, and Robert Waterston from July 16 to 19, as part of the Genentech Center for the History of Molecular Biology and Biotechnology program. Prominent researchers participating in DNA sequencing from its beginnings were brought together to describe how the technology developed, its effect on the biological sciences, and its role in current and future research.

Other highlights of 2015 included:

- Hermann Muller Exhibition, February
- Exhibit and website honoring the Albert Lasker Basic Medical Research Award to Evelyn Witkin for discoveries regarding the DNA-damage response

- James D. Watson lecture "Celebrating 50 years of Molecular Biology of the Gene"
- Women in Science Exhibition, October

Trustees

G.D. Yancopoulos

George D. Yancopoulos, M.D., Ph.D., Chief Scientific Officer of Regeneron Pharmaceuticals, Inc. and President of Regeneron Laboratories was elected to the Board of Trustees.

Dr. Yancopoulos joined Regeneron in 1989 as its Scientific Founder and is currently Chief Scientific Officer and President of Regeneron Laboratories. Together with key members of his team, he is a principal inventor and developer of Regeneron's four FDA-approved drugs—Praluent (alirocumab) Injection, Eylea (aflibercept) Injection, Zaltrap (ziv-aflibercept) Injection for Intravenous Infusion, and Arcalyst (rilonacept) Injection—as well as of Regeneron's foundational technologies for target and drug development, such as its proprietary TRAP technology, VelociGene and VelocImmune.

In the 1990s, Dr. Yancopoulos was the 11th most highly cited scientist in the world, and in 2004 he was elected to both the National Academy of Sciences and the American Academy of Sciences. Dr. Yancopoulos has long-term ties to the CSHL. Together with his Ph.D. mentor, Dr. Frederick W. Alt, who now heads the CSHL Scientific Advisory Board, he taught the CSHL cloning course for many summers in the 1980s.

Development

More than $4.5 million was raised at the 10th Double Helix Medals dinner (DHMD) in November. The gala was held for the first time at the American Museum of Natural History (AMNH) in New York City and honored Katie Couric, Anne Wojcicki, and David Botstein, champions of research to benefit mankind.

The 14th annual Women's Partnership for Science luncheon was held in September, featuring guest speakers Anja Hohmann and Maria Nattestad, Watson School Ph.D. students. Since 2002, the event has raised $1.5 million for pioneering research. This year's event included a special honor for enthusiastic Laboratory supporter, Cathy Soref. Cathy has been part of the CSHL community for more than 25 years. In 2006, Cathy initiated the Double Helix Medals dinner.

Double Helix honorees Katie Couric, David Botstein, and Anne Wojcicki with CSHL President Bruce Stillman

Cathy Soref, pictured with CSHL President Bruce Stillman and Watson School students Anja Hohmann and Maria Nattestad, was honored at the 2015 Women's Partnership for Science lunch.

Double Helix Meeting; *DNA Damage, Repair & Mutation*

CSHL's 22nd annual golf tournament raised $230,000 for research and education honoring Trudy and Tom Calabrese—former CSHL Association President and founding CSHL Corporate Advisory Board member, respectively.

Cold Spring Harbor Laboratory (CSHL) was among 17 Long Island–based organizations to receive funding from the 2015 Long Island 2 Day Walk to Fight Breast Cancer. The $19,000 donation received by CSHL will support breast cancer research in the laboratory of Professor Alea Mills, Ph.D. In addition to its participation in the events, CSHL heads The LI2DAY Walk Scholarship Committee, which awarded six $2500 scholarships to Long Island high school seniors who have a parent or guardian with breast or other women's cancer.

A special thank you this year to Chancellor Emeritus James D. Watson and his wife Liz, who donated $1 million to the Laboratory in support of biomedical research and education programs. To date, Jim and Liz have donated more than $5 million to the Lab in addition to many other invaluable contributions, ensuring the Lab's leadership in contemporary biology and genetics research and education.

The Watson gift includes an endowment to support a special annual scientific meeting called "Double Helix Day," in memory of February 28, 1953—the day that Watson and his colleague Francis Crick discovered the double helix structure of DNA.

Community Outreach

CSHL Public Lectures—Special 125th Anniversary Series

May 3—Silvia Earle, Ph.D., National Geographic Explorer in Residence; *Saving Our Oceans*.

June 17—Michael Wigler, Ph.D., Professor, Cold Spring Harbor Laboratory; *Seeking Out Cancer*; co-sponsored by CSHL, US Trust—Bank of America, North Shore-LIJ and St. Johnland Nursing Center.

S. Earle

October 4—Harold Varmus, M.D., Weill Cornell Medical College; Nobel Laureate; Former Director, National Cancer Institute; *Biomedical Research: Then and Now*.

October 13—Peter Neufeld, Co-founder and Co-director of the Innocence Project; *How the Lessons of DNA Transform Criminal Justice*, 2015 Lorraine Grace lectureship on societal issues of biomedical research.

October 29—David Spector, Ph.D., Professor and Director of Research, Cold Spring Harbor Laboratory; *Searching for New Ways to Halt the Progression of Breast Cancer*; hosted by Mather Hospital as part of Paint Port Pink events in Port Jefferson, New York.

November 8—David Tuveson, M.D., Ph.D., CSHL Professor, Lustgarten Foundation Director of Research; **Craig Devoe, M.D.**, Chief, Hematology and Medical Oncology, The Monter Care Center, North Shore-LIJ; *A Partnership to Defeat Pancreatic Cancer: CSHL & The Lustgarten Foundation*.

November 12—Stephen Shea, Ph.D., Associate Professor, Cold Spring Harbor Laboratory; *Cocktails & Chromosomes* Inaugural event at Finley's of Greene Street in Huntington, New York.

November 16—Neil Shubin, Ph.D., Robert R. Bensley Professor, Organismal Biology and Anatomy, University of Chicago; *Your Inner Fish.*

I.M. Yang

CSHL Public Concerts—2015

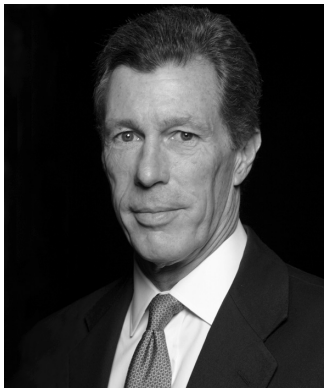
March 27—Martin Kasik, piano
April 17—Jiayin Shen and Alan Woo, piano duo
May 1—Julia Bullock, soprano (with piano)
May 15—Trio Solisti, violin, cello, and piano
August 21—Southampton Arts Festival Chamber Orchestra
September 11—In Mo Yang, violin (with piano)
September 18—Ko-Eun Yi, piano
October 2—Mei Rui, piano

Looking Forward

Thank you to our faculty, students, and staff for their hard work this anniversary year. History offers us pride and inspiration as we all look forward to continuing CSHL's leadership role in molecular biology and genetics research and education.

Bruce Stillman, Ph.D., F.R.S.
President and Chief Executive Officer

CHIEF OPERATING OFFICER'S REPORT



As Bruce Stillman rightly points out in his President's Report, basic discovery science, the heart of Cold Spring Harbor Laboratory's mission, is becoming increasingly expensive. This is a result of many factors, including escalation in expenses associated with scientific equipment, supplies, and recruitment and retention of the world's best scientists. Unfortunately, this upward expense spiral has coincided with a 20% inflation-adjusted decline in the budget of the National Institutes of Health over the last decade.

CSHL has navigated its way through this challenging environment by excelling in a few critical areas. One of those is the success of our faculty in obtaining federal grants. Over the last year, their success rate was 46% as compared to the national average of 17%. This is simply a reflection of the excellence of our research and the vigor with which our investigators, in partnership with our Office of Sponsored Programs, write and submit high-quality federal grant applications. In other words, we continue to obtain a bigger slice of a shrinking pie.

At the same time, the Laboratory has been very successful in attracting funds from private foundations and philanthropy. One need only look at the shift in the mix of our research funding over the last decade. In 2005, federal grants made up nearly 60% of the total, with private sources at 20%. Ten years later in 2015, federal grants constitute 44%, with private sources at 29%. It is important also to note that the remaining 27% of the research budget is now funded by Laboratory sources, including the annual fund and spending from our endowment funds, both of which are reflective of a highly energetic and successful fundraising effort. For this we have to thank our Development Office, our Board of Trustees, and the many devoted supporters of CSHL.

The Laboratory's endowment fund, in some respects its lifeblood, has grown impressively from $215 million in 2008 to $450 million at year-end 2015. This growth is the result of many generous endowment gifts in addition to investment returns on the funds. Since the 2008 financial crisis, we have benefitted from strong financial markets and a sound investment strategy developed by the Investment Committee of our Board of Trustees. While in calendar year 2015 CSHL investment returns were flat, we have not had a down year in the last seven and in four of those years we achieved double-digit returns. This combination of fundraising and positive investment returns is inarguably good news. However, as stock markets hover near all-time highs and interest rates remain stubbornly low, it is increasingly difficult to plan for investment returns on the endowments that are substantially in excess of our spending rate. This is a challenge now being addressed.

So we are doing many things well at the Laboratory and, as a result, are on much firmer financial footing than many of our peer institutions. However, there is a big-picture concern over which we have less control. This problem was well articulated by honorary degree recipient Senator Tom Harkin, who delivered the commencement address at the 2016 Watson School graduation ceremony. Citing the decline in federal research funding, the senator expressed deep concern over the antiscience discourse in the United States. In his words, "I think there is a clear and present danger that the U.S. will lose its leadership in the years ahead. This will have a devastating impact across our economy with lower growth and fewer innovations. We must put a stop to the growth of the tumor of anti-intellectualism and antiscience in our body politic."

Strong words for sure, but a warning worth heeding. If we become a society where dogma and beliefs supplant empirical evidence and facts, it will be difficult even for institutions as fine as Cold Spring Harbor Laboratory to thrive.

W. Dillaway Ayres, Jr.
Chief Operating Officer

Long-Term Service

Front row (*left to right*): Leemor Joshua-Tor, Lisa Manche, Madeline Wisnewski, James Watson, Beicong Ma, Jodi Coblentz, Alyson Kass-Eisler, Linda Rodgers; *back row* (*left to right*): William Bishop, Barry Burbach, Ronald Romani, Benjamin Veneable, Bruce Stillman, David Spector, Hock Yew Teo, George Newell, Dill Ayres.

The following employees celebrated milestone anniversaries in 2015:

45 years	Madeline Wisnewski
35 years	Linda Rodgers
30 years	Lisa Manche, David Spector
25 years	Edward Campodonico, Clare Clark, Beicong Ma, George Newell, Barbara Purcell, Ronald Romani, Hock Yew Teo, Nicholas Tonks
20 years	William Bishop, Barry Burbach, Giuditta Carino, Kenneth Chang, Jodi Coblentz, Joshua Dubnau, Leemor Joshua-Tor, Alyson Kass-Eisler, Mary Muno, Mona Spector, Benjamin Veneable

Front row (*seated left to right*): Elna Carrasco, Jill Stone, Yi Jun Sheu; *middle row* (*left to right*): Michael Ronemus, Xiaoqun Zhang, Mary Sabala, Leo Greene, John Schindler; *back row* (*left to right*): James Decker, Charles Prizzi, Bruce Stillman, Wesley Dreusike, Denise Roberts, David Spector, Dill Ayres.

15 years	Paula Abisognio, Carol Brower, Amy Burrows, Elna Carrasco, James Decker, Wesley Dreusike, Jeffrey DuPree, Suzanne Esposito, Leo Greene, Matthew Hoyer, Z. Josh Huang, Charles Prizzi, Denise Roberts, Michael Ronemus, Mary Sabala, John Schindler, Yi-Jun Sheu, Jill Stone, Peter Van Buren, Xiaoqun Zhang, Steven Zielinski