CSH Cold Spring Harbor Laboratory

2015 ANNUAL REPORT

Executive Summary

Cold Spring Harbor Laboratory (CSHL) is a private, not-for-profit research and education institution at the forefront of efforts in molecular biology and genetics to generate knowledge that will yield better diagnostics and treatments for cancer, neurological diseases, and other major causes of human suffering.

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Executive Summary

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Front cover
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Basic research is a central, defining activity of Cold Spring Harbor Laboratory. It is the wellspring of both new knowledge and technological advances that make new discoveries possible.

This discovery science is expensive, and getting more expensive every year. Inflation in the biomedical sector outpaces that of the broad US economy, mostly due to the wide use of advanced technologies that require expensive equipment or reagents. We also pay a premium for the highly trained personnel who are needed to offer ever increasingly high-tech methods to our faculty, postdoctoral fellows and students. At the same time, we continue to see an erosion of the total amount of support any highly meritorious scientist can obtain from federal sources such as the National Institutes of Health and the National Science Foundation. At the NIH and NSF, policies implemented in the last four years have deliberately limited the type and amount of funding that can be awarded to the nation's very best and most productive scientists in order to "spread the grants as widely as possible," a form of scientific socialism that does not bode well for the future of American science. At the same time, however, opportunities abound in many areas of science, including cancer, neuroscience, plant biology and quantitative biology—areas of focus at Cold Spring Harbor.

Fortunately, with very strong support from our Board of Trustees and supporters of CSHL, we have seen a dramatic increase in our endowment. But this precious resource should support the core of what makes CSHL one of the leading research institutions in the world of basic discovery science. Having recognized this, it has been increasingly obvious that there are many instances in which we can add value to our science and translate these discoveries they will make an impact in the clinic —and this is particularly the case for cancer.

With this background, we took the initiative in 2015 of entering into a strategic affiliation with Northwell Health, previously known as the North Shore-LIJ Health System. It's an alliance that I expect to be transformative. It will provide an unprecedented opportunity to add value to certain of our discoveries and multiply the impact of our research.

CSH Cold Spring Harbor Laboratory 1890 125 2015

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Northwell Health℠

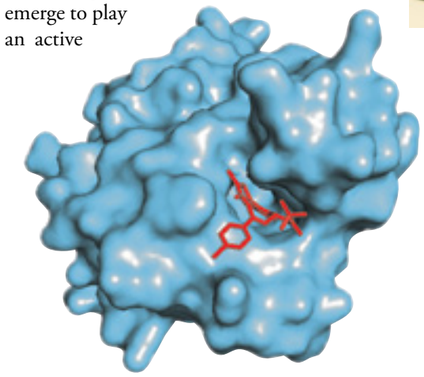
The urgency of speeding the translation of basic research into clinical advances is captured in this picture of pancreatic cancer patient Gail Poinelli conferring with CSHL's Dr. David Tuveson (right) and Northwell Health's Dr. Craig Devoe. The brave Ms. Poinelli, who lost her battle with the illness in 2016, is one of over 40,000 Americans whose lives are claimed by pancreatic cancer annually.

The sweet spot of the affiliation is translational cancer research, which includes the development of new cancer diagnostics and therapeutics and the training of a new generation of research-capable cancer clinicians. Northwell Health is one of the largest integrated health systems in the nation. Its recently expanded Cancer Institute, with over 200 academic oncologists and clinicians, is part of a system of care encompassing 21 hospitals and 400 outpatient physician practices throughout the New York metropolitan area. Serving more than 8 million people, Northwell treats some 19,000 new cancer cases annually. This makes it one of the most important sites of cancer treatment in the US.

As CEO Michael Dowling has noted, Northwell's oncologists will make CSHL's most promising pre-clinical research available to cancer patients in the form of innovative trials. Patients will be receiving advanced treatments and diagnostics they would not otherwise be offered, and benefit from them years before they would be available to patients elsewhere. At the same time, Northwell's large patient intake provides our scientists with opportunities to perform cancer research using tumor samples from precisely defined subsets of patients. As we move further into the era of targeted therapy, assembling appropriate patient cohorts becomes ever more critical if we want to speed the time it takes to evaluate new treatments.

Clinician-scientists at Northwell have already begun teaming up with faculty at CSHL. Each team has a specific disease focus, or a focus within broad types of cancer such as particular subtypes of breast or prostate cancer. Under the leadership of Dr. David Tuveson, deputy

director of CSHL's NCI-designated Cancer Center and a talented clinician-scientist, Northwell-CSHL teams have begun to gather periodically at our Banbury Center to plan and assess their work. Our agreement additionally supports the education and training of Oncology Fellows. In this aspect of the alliance, the clinical training of oncologists in the Northwell Health system, in conjunction with the Hofstra University-Northwell Health School of Medicine, will include an elective period of laboratory research at CSHL. Via summer and full-year fellowships, a cadre of cancer doctors in training will emerge to play an active role in translating the next wave of fundamental discoveries about cancer into new diagnostics and therapies.

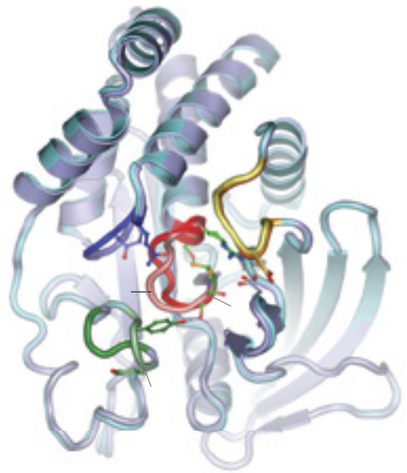


Christopher Vakoc (above) and colleagues in 2011 discovered a powerful drug target called BRD4 for AML, an often deadly form of leukemia. Translational work has already led to clinical trials testing the effectiveness of a drug called JQ1 (red) that "hits" the target (left).

It's reasonable to ask how the new alliance will change the way research is done at CSHL. I want to make clear that it in no way alters our core commitment to basic research, which is unshakable. This collaboration adds to our capabilities in a manner illustrated by two contrasting stories about basic research. One of these stories came to a happy conclusion early in 2015 when the Food and Drug Administration approved palbociclib (Ibrance) for the treatment of metastatic breast cancer. It's a first-in-class inhibitor of CDK4 and CDK6, enzymes called protein kinases that help regulate the cell division cycle. In 1991, David Beach, then a highly productive CSHL basic scientist who had already published many papers helping to identify the molecular players involved the control of cell division, reported the discovery of yet another factor, which he called Cyclin D. This discovery coincided with the same finding by former CSHL Trustee Charles Scherr of St. Jude's Children's Hospital, who went on to discover the protein kinase CDK4, which forms a complex with Cyclin D. It soon became clear from the work of Beach and Scherr that the Cyclin D-CDK4 complex is a critical node in the fundamental decision of whether a cell keeps dividing or rests from proliferation. Importantly, it became apparent that most cancer cells have mutations in this control pathway, thereby pushing tumor cells on the road to unchecked growth and aggressive cancer.

...our commitment to basic research is unshakable.

What is poignant about the 2015 approval of Ibrance is the fact that it came a quarter-century after the fundamental discoveries by Beach and Scherr. In the early 1990s, we simply did not know enough about cancer to convert their newly generated knowledge into an effective anticancer drug. Now we do. Another basic research discovery at CSHL, this one quite recent, makes the point about our progress vividly, suggesting why the time is ripe for a clinical alliance that enhances our ability to promptly take our basic insights into the clinic. In 2011, Christopher Vakoc, Scott Lowe and CSHL colleagues performed a screen using RNA interference (RNAi) technology developed at CSHL by Gregory Hannon and his team. The 2011 discovery, which Vakoc has carried forward, revealed a drug target—a protein called BRD4—of unusual potential in the treatment of aggressive forms of leukemia called acute myeloid leukemia (AML). Vakoc discovered that a drug—developed for another purpose by collaborating scientists at the Dana Farber Institute—hit the target, virtually eliminating AML in mouse models. These studies induced a number of pharmaceutical and biotech companies to initiate clinical trials that target AML, some of which are now in Phase II, with positive results already reported from Phase I studies. This is precisely the kind of rapid translation of an important basic scientific result that our new alliance with Northwell Health and its vast clinical system is designed to facilitate. It will enable us to pursue translational science with a vigor we otherwise could not while keeping our basic discovery engine primed.



Two of our faculty are now reaping the rewards of decades of meticulous basic research. Adrian Krainer's research on RNA splicing—which began in the 1990s and grows out of earlier Nobel Prize-winning work by Louise Chow and Richard Roberts at CSHL and by Sue Berget and Phillip Sharp at MIT—has made possible the development of a drug, now in Phase III trials, for the serious

The power of basic research is exemplified in discoveries made by Nicholas Tonks and his team. Twenty-five years ago Tonks discovered an enzyme called PTP1B (illustration above) that is now the focus of several drug development efforts with potential applications in breast cancer, diabetes, obesity and Rett syndrome.

children's disease, spinal muscular atrophy (SMA). Nicholas Tonks' fundamental discovery 25 years ago of the first of what proved a large family of enzymes called protein tyrosine phosphatases (PTPs) was the beginning of a scientific odyssey in which Nick has persisted in the face of doubters in the pharmaceutical industry. Tonks' team has recently demonstrated their ability to target PTP1B—with a drug Nick developed years ago—in cellular signaling pathways that play a key role in HER2-positive breast cancer. Phase 1 trials will begin at Northwell in the spring of 2016. Other PTP1B-targeting compounds in Tonks' lab are being evaluated by a major pharmaceutical firm for treatment of diabetes and obesity. It's another illustration of how basic science can pay off in ways that are not contemplated at the outset. We see similar promise in other fields: for instance, in Zachary Lippman's basic research on the process of branching morphogenesis in plants, which now points to a way of significantly increasing fruit yields; and in Steven Shea's fundamental research on social behavior in rodents, which has led to unexpected insights into Rett syndrome, an autism spectrum disorder.

Basic research in plant biology in several CSHL labs has led to discoveries that have the potential to significantly increase the yield of tomatoes, maize, and other food crops.

Basic research has made all of these opportunities possible. To keep our discovery science robust, we were pleased this past year to have been asked to join the ranks of select institutions named as beneficiaries of the Scientific Philanthropy Alliance. The SPA serves as an impartial advisor to major philanthropists, promoting basic research as the driver of new ideas, of new economic wealth and for the education of a new generation of talented new scientists. Several benefactors of the Laboratory organized the SPA, which we thank for providing another line of support for the basic research that is the lifeblood of Cold Spring Harbor Laboratory.

April 2016

RESEARCH

CANCER

Researchers at CSHL are devoted to understanding the fundamental biology of human cancer. Their commitment to studying basic cellular processes reflects the premise that understanding how these processes are altered in cancer cells will provide a framework for rational therapies. Several technological advances developed at the Laboratory have given rise to innovative genomic approaches and the development of new mouse models of various cancer types. These provide a powerful pathway for discovery, characterization, and validation of genes that contribute to cancer development and progression. A unique aspect of the CSHL cancer program is its cooperative nature. Scientists are encouraged to share their ideas and work on questions across labs, in a synergistic way that far exceeds the power of any single laboratory working in isolation. CSHL has been designated as a Cancer Center of the National Cancer Institute since 1987.

NEUROSCIENCE

CSHL neuroscientists focus on understanding how neural activity and neural circuitry underlie behavior, and how disruptions in these circuits lead to neurological and neuropsychiatric disorders such as Alzheimer's disease, autism, schizophrenia, and depression. These questions are addressed in two model systems—rodents and fruit flies—using molecular, cellular, genetic, developmental, theoretical, physiological, and behavioral approaches. Neuroscience research at CSHL is highly collaborative and can be divided into three broad themes: sensory processing, cognition, and cognitive disorders. In addition, there is an effort to develop new anatomical methods to improve our understanding of brain circuits, connectivity, and function.

PLANT BIOLOGY

The plant group at CSHL studies fundamental mechanisms in plant development and genetics that impact crop productivity, biodiversity, climate change, and the development of biofuels. Their research uses *Arabidopsis*, maize, and most recently tomato as model systems, and it expands upon the Nobel Prize–winning work done at CSHL by Barbara McClintock in the 1940s and 1950s. The transposable genetic elements, or "jumping genes," that she discovered are now understood to reprogram the epigenome and are being used at CSHL for functional genomics in *Arabidopsis* and maize. CSHL has taken part in numerous plant genome-sequencing projects including *Arabidopsis*, rice, sorghum, and maize, as well as epigenomic sequencing and profiling.

GENOMICS

The Genomics Program is composed of faculty working across disciplines and research areas. Its main research interests are genomic organization; structural variation of the human genome as related to disease; computational genomics and transcriptional modeling; and sequencing technology. Program facilities are located at the main campus and a few miles away at the Woodbury Genome Center. The investigators conduct research in the areas of human genetics, functional genomics, small RNA biology, and bioinformatics.

QUANTITATIVE BIOLOGY

CSHL's Simons Center for Quantitative Biology (SCQB) brings to questions in biological science the insights of applied mathematics, computer science, theoretical physics, and engineering. Members of the SCQB interact closely with other CSHL researchers and apply their approaches to research areas including genomic analysis, population genetics, neurobiology, evolutionary biology, and signal and image processing.

CANCER
NEUROSCIENCE
PLANT BIOLOGY
GENOMICS
QUANTITATIVE BIOLOGY

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- Gurinder Atwal
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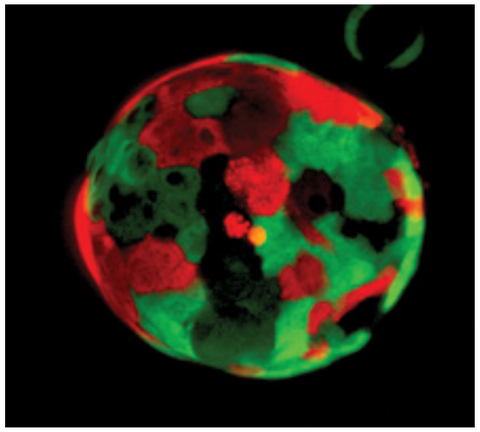
- Marja Timmermans
- Jessica Tollkuhn
- Nicholas Tonks
- Lloyd Trotman
- Glenn Turner
- David Tuveson
- Christopher Vakoc
- Linda Van Aelst
- Doreen Ware
- Michael Wigler
- Anthony Zador
- Lingbo Zhang
- Hongwu Zheng
- Yi Zhong

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 as well as the scope of the faculty's research interests are suggested in this sample of a few of the past year's important findings.



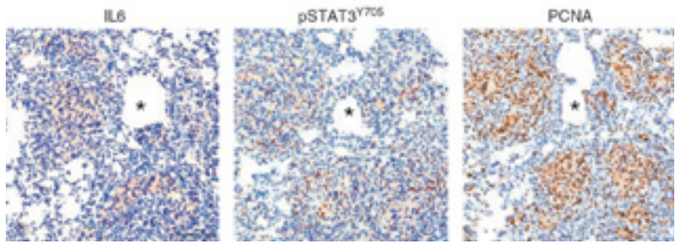
A pancreatic organoid grown in the Tuveson lab.

Organoids to aid pancreatic cancer research

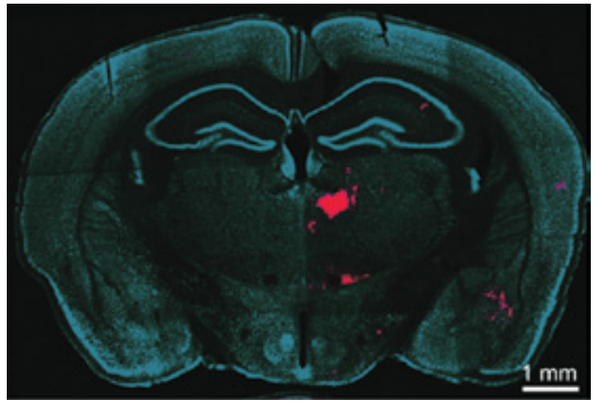
All cancer research relies on a steady supply of cells, both normal and cancerous, that can be grown in the laboratory. By comparing normal cells to cancer cells, scientists can identify changes that lead to disease. Yet both types of pancreatic cells have been difficult to culture in the laboratory. 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 3-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

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, since patient responses to hormone therapy vary widely, and it's 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.



Lung tissue (blue) colonized by prostate cancer cells. Brown areas indicate, from left to right, the presence of IL-6, an immune system component and possible biomarker, its downstream target STAT3, and PCNA, a marker of metastasis.



In this coronal view of mouse brain, red fluorescence is generated by inhibitory neurons in the PFC; it illuminates any neurons providing input into them—implying a direct connection with red-labeled neurons in the thalamus.

Brain circuit implicated in schizophrenia

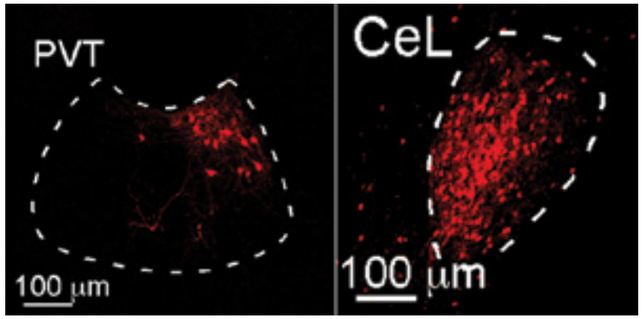
The prefrontal cortex (PFC) plays an important role in cognitive functions such as attention, memory and decision-making. Faulty wiring between the PFC and other brain areas is thought to give rise to a variety of cognitive disorders. Disruptions to one particular brain circuit—between the PFC and another 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 feedforward 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 feedforward 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 which 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.

How a brain circuit controls fear

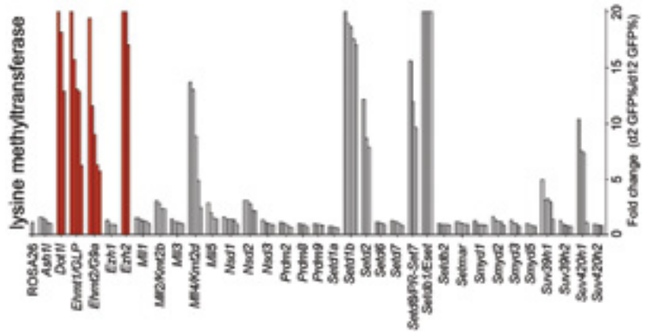
It is hard to imagine that an intangible emotion like fear is encoded within neuronal circuits, but Bo Li and colleagues have found that fear is stored within a distinct region of the brain. In recent years, they have discovered that fear learning and memory are orchestrated by neurons in the central 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 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.



Red cells are neurons identified by a method enabling researchers to trace circuits between two brain regions—here, the PVT (in the thalamus) and CeL (in the amygdala).

Mastering CRISPR to reveal cancer targets

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 upon in order 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.



A "Manhattan plot" showing 4 already-known drug targets in leukemia (red spikes) identified in a single CRISPR screen, along with several others not previously discovered (grey spikes).

Our probabilistic approach to numbers

Humans, including pre-verbal babies and adults in indigenous cultures with no formal mathematical education, are capable of estimating numbers of objects. Yet while 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 audio-visual 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.

Reversibility of Rett syndrome symptoms

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 lifespan 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 vigorously pursue.

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

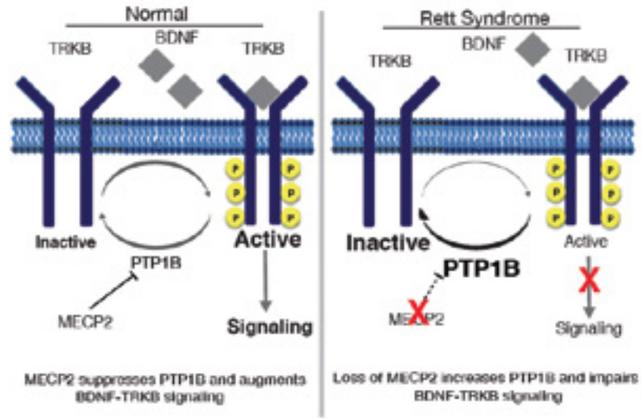


Diagram illustrating how experimental drug developed in Tonks lab inhibits PTP1B in mice modeling Rett syndrome, by releasing the brake on BDNF-TRKB signaling.

More stem cells in the meristem (bottom row) correspond with more flowers (top row) and larger fruit (middle). The Lippman lab identified a set of genes that controls stem cell production in tomato.

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.

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. 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.

The Martienssen lab solved a decades-old mystery, explaining the epigenetic factors that cause oil palm clones to grow into trees that yield desiccated "mantled" fruit (right) instead of healthy fruit (left).

EDUCATION

In 1890, **high school biology** teachers took courses at Cold Spring Harbor under the aegis of the Brooklyn Institute of Arts and Sciences. The Laboratory's "phage" courses of the post-World War II years were intellectual incubators for the pioneers of molecular biology. Today, CSHL carries forward this tradition in a remarkable range of educational offerings for working scientists, scientists in training, and students and teachers in primary and secondary school systems locally, throughout the United States and overseas.

MEETINGS & COURSES PROGRAM

CSHL's reputation as one of the world's premier hubs of activity in biology and genetics is linked to its Meetings & Courses Program. With roots in the legendary annual Symposia in Quantitative Biology series, which began in 1933, the program organizes more than 60 meetings and courses annually, covering a wide range of topics in the biological sciences. Together, they bring some 9000 scientists to the Long Island campus each year. Participants range from the most accomplished senior investigators to graduate students and postdocs. Programs are put together on the basis of openly submitted abstracts and include the discussion of unpublished work. A CSHL-styled meetings program that began in 2009 thrives in Suzhou, China.

BANBURY CENTER

Banbury Center, located on the grounds of the historic Robertson House, provides opportunities for scientists and other leaders in society to discuss topics of common interest. About two dozen meetings are organized at Banbury each year, for groups of up to 40 invited participants. These are recognized internationally as being among the best discussion workshops for topics in molecular biology, molecular genetics, human genetics, neuroscience, and science policy.

WATSON SCHOOL OF BIOLOGICAL SCIENCES

The Watson School of Biological Sciences (WSBS) trains the next generation of biologists, offering the Ph.D. in biology in as little as 4 years to a limited number of highly accomplished students drawn from around the world. The curriculum is designed to train self-confident, self-reliant young scientists to become scholars and to acquire the knowledge that their research and future careers demand. The accomplishments of WSBS students have been spectacular, with more than 250 papers published in the 15 years since the school's launch. Graduates have moved swiftly into faculty positions at leading academic research institutions worldwide.

DNA LEARNING CENTER

The DNA Learning Center (DNALC) has a major impact not only in the New York metropolitan area, but also globally in pioneering public science education for the genome age. With teaching facilities in Long Island and New York City, it brings a hands-on approach to learning about biology and genomes to classrooms and homes of children in primary schools, middle schools, and high schools. Renowned for devising means for young people, teachers, and parents to conduct sophisticated experiments with DNA, the DNALC also has a robust presence on the Internet, powered by a team of multimedia innovators who bring knowledge of the life sciences to computer, tablet, and cellphone users.

COLD SPRING HARBOR LABORATORY PRESS

With origins in the 1930s, CSHL Press enhances the Laboratory's educational mission by publishing original work that assists in the advance and spread of scientific knowledge. Sale of its publications enhances the Laboratory's international reputation for excellence. The Press publishes research and review journals, books, manuals, primers, and other information sources, in electronic and print form. Widely reviewed and highly praised, these publications are made available in a variety of languages.

Meetings & Courses Program

Cold Spring Harbor Laboratory's reputation as one of the principal crossroads of biology can be attributed to the enormous success of its Meetings & Courses Program. With roots in the famous Cold Spring Harbor Symposia series, dating to 1933, the program currently encompasses some 55 meetings and 30–35 lab and lecture courses held over two-year cycles. Since 2009, a parallel program of meetings has been held in Suzhou, China, under the aegis of the Cold Spring Harbor Asia program, a wholly owned subsidiary of the Laboratory.

In 2015 the CSHL Meetings attracted almost 7,600 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. It drew over 400 participants from around the globe and was reported in the journal *Science*.

In June, Cold Spring Harbor Asia Conferences hosted a special meeting in Suzhou, bringing together stakeholders in many of the national brain projects initiated around the world over the last one to two years. This meeting, too, was the subject of a detailed article in *Science*.

The Courses program covers a diverse array of topics in molecular biology, neurobiology, structural studies and bioinformatics. Over 750 instructors, lecturers and assistants come to teach at CSHL from universities, medical schools, research institutes and companies around the world. In 2015 about 700 trainees—who included advanced graduate students, postdocs and faculty—attended courses lasting from one to three weeks.

The Courses program relies heavily upon grants and foundation support. 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. The Helmsley Interdisciplinary Fellowship Fund provided major funding to almost 100 scientists to participate in CSHL courses outside their primary disciplines. The Courses also benefit from the loan of equipment, donation of reagents and technical support from many companies, whose support is indispensable to ensure that the program remains cutting-edge.

Banbury Center

2015 was very busy at the Banbury Center, the Laboratory's "think-tank" for biology and science-and-society issues located on the former Robertson estate in Lloyd Neck, across the harbor from the main campus.

This year, Banbury meetings attracted over 600 participants. One highlight occurred in March, when "Exercise Science & Health" 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 & 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 doesn't 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.

In 2015 the Banbury website added short reports of the meetings, as well as descriptions of classic Banbury meetings. These can be accessed from the home page www.CSHL.edu/banbury. This year's meetings, as those of past years, were made possible in significant part by generous support of corporate sponsors and underwriters.

Banbury Conference Center 2015 meeting "HIV-1 & How to Kill a Killer."

Watson School of Biological Sciences

In 2015 the Watson School welcomed its 17th incoming class and graduated its 12th. The achievements of the graduate program continued to grow. The quality of scientific publications produced by the school's students remained highly impressive. Watson School 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. Graduates have also moved into influential positions in administration, publishing, consulting and industry.

WSBS entering class of 2015.

The Watson School is known for its unusual commitment to faculty mentoring. Students benefit from a two-tiered mentoring approach, in which each receives an academic as well as a research mentor. The academic mentor is selected first, and provides counsel during the intensive coursework of the first term, and also during lab rotation periods, at the end of which students identify and select a suitable research mentor. The academic mentor remains active, serving as sounding board and advocate for students as they work toward their doctoral degree.

At the 2015 graduation ceremony, 12 WSBS students were awarded Ph.D. degrees, bringing the total since the school's inception to 83. The new graduates are: Özlem (Mert) Aksoy, Mitchell Bekritsky, Sang-geol Koh, Nilgün Taşdemir, Elvin Wagenblast, and Susann Weissmueller from the Entering Class of 2008, Stephane Castel, Kristen Delevich, Wee Siong Goh, Ian Peikon and Cinthya Zepeda Mendoza from the Entering Class of 2009, and Jack Walleshauser from the Entering Class of 2010. Michael Giangrasso from the Entering Class of 2013 was awarded a Master's degree. During the year, scientific papers published by students of the school appeared in major journals, bringing the cumulative total to over 300. Current and former students won prestigious and highly competitive scholarships and fellowships, as in past years.

In August, seven new students entered as Members of the Class of 2015. They were selected from among 310 applicants and represent the United States, Lithuania, Russia, the United Kingdom, and Vietnam. Other new graduate students entered as visitors from other institutions, including seven from Long Island's Stony Brook University; other current visitors hail from more distant institutions, including Cornell University and National Centre for Biological Sciences, India.

From June through August, 20 undergraduates from across the U.S., as well as China and Switzerland, took up residence at CSHL to take part in the historic Undergraduate Research Program. These "URPs" (chosen from among 1,047 applicants) had the remarkable opportunity to perform advanced research in the laboratory of a CSHL faculty member. The URP Program along with the equally innovative Partners for the Future program, which brings gifted local high school students to CSHL labs for hands-on research experience, are run and managed by the Watson School.

The Ötzi exhibit at the DNALC has been extremely popular with students.

DNA Learning Center

The DNA Learning Center (DNALC) is a world leader in providing education that prepares students—as well as their teachers and even family members—to thrive in the genome age. When the DNALC was founded in the late 1980s, the idea of sequencing genomes was just a gleam in the eyes of a handful of visionary biologists. Among them was then Laboratory Director James D. Watson, who provided the impetus for a young staff to develop what has since become a trademark hands-on approach for introducing young people to a revolutionary new science.

The DNALC's glowing reputation is partly the fruit of having instructed over half a million Long Island and New York metropolitan area students over the last quarter-century. But it also stems from the program's success in carrying its instructional methods to far corners of the earth. In 2015, the DNALC concluded negotiations to develop a DNA Learning Center Asia in Suzhou Industrial Park, near Shanghai, China. It's the high point of a licensing program that began in 2002, which has led to licensed centers in Singapore (2003), Vienna (2006), Notre Dame University (2013), Beijing 166 High School (2014) and Mexico City Health Park (2014). DNALC Asia has been registered as an "internal" Chinese NGO, sponsored by CSH Asia Conferences. It's 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 in Cold Spring Harbor Village.

Closer to home, 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 8,908 students completed labs in their own schools, led by DNALC staff, while 1,348 students attended week-long summer camps. The Center's popular Urban Barcode Project had a successful 4th year, with participating students presenting research posters and giving oral presentations at the American Museum of Natural History. The program trains teachers to be mentors for their students engaged in projects; the related Urban Barcode Research Project, this year involving students from 30 public and 10 private high schools, brings students under the direction of scientist-mentors. 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. Monthly *Saturday DNA!* Sessions drew 229 participants, with parents and grandparents joining children for classes on natural selection, bacteria and antibiotics, and genetic engineering, among other topics.

The year's highlight was the opening of an exhibit at the Dolan DNALC several years in the making. Featuring a precise life-size reproduction of "Ötzi the Iceman," the mummified remains of a European male who lived about 5,300 years ago, the exhibit provides the entry point for exploration of human origins, a longtime interest of the center. Ötzi, in fact, joined an articulated Neanderthal skeleton and grave cast, a bust recreation of Homo erectus, and skulls of 16 ancient hominids on display. Altogether, these exhibits are 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.

Ötzi—whose actual remains are on display in a museum in the Italian Alps—is in fact the subject of what is perhaps the world's oldest actively investigated murder mystery. He was killed on a mountain slope over 10,000 feet above sea level, by an arrow entering his upper body from the rear. The story was first told in an episode of the popular PBS science program NOVA in 2012. Under development in 2015, a new installment in the series, called "Iceman Reborn," will focus on the creation of the Ötzi replica now on display at the Dolan DNALC.

Cold Spring Harbor Laboratory Press

Scientists from around the world have exchanged data and ideas at Cold Spring Harbor Laboratory since its first Annual Symposium more than 80 years ago. The Laboratory's Press extends the opportunity to communicate what's new and exciting through its growing list of journals, books, manuals, and digital tools. The goal is to provide scientists with information that is appropriate, authoritative, and affordable.

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. *Genome Research* and *Genes & Development* remain in the topmost ranks of journals in their fields. *RNA* and *Learning & Memory* provide value for more specialized research communities. *Perspectives* and *Protocols* gain ground and usage as essential library assets. Online, the Press journals had a record download of more than 13.4 million full-text articles.

Interest in print books is falling among scientists—but under the right circumstances, as in 2015, there can still be sufficient demand to make book publishing financially viable. The best sellers were newly released volumes devoted to the intricacies of epigenetics and the computational analysis of genome sequencing, as well as two perennial favorites, *At The Bench*, an initiation into experimental science, and the classic compendium of lab techniques, *Molecular Cloning*.

In 2015, the Press built a new distribution platform that permits direct sales of e-books to individuals and research groups. This new approach has proved popular and will be adopted for many future titles.

A highlight of the year was the 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 over 1,500 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.

An editorial team at the Press at work on a manuscript.

COLD SPRING HARBOR LABORATORY CONFERENCES

	Title	Organizers
Jan. 28–Feb. 1	Systems Biology: Global Regulation of Gene Expression	Tim Hughes, Christina Leslie, John Stamatoyannopoulos, Sarah Teichmann
March 3–6	Cellular Dynamics & Models	Jennifer Lippincott-Schwartz, Wallace Marshall, Ed Munro, Vito Quaranta
March 17–21	Systems Biology: Networks	Pascal Braun, Suzanne Gaudet, Ben Lehner, Chad Myers
March 24–28	Wiring the Brain	Joshua Huang, Kevin Mitchell
April 8–11	RNA & Oligonucleotide Therapeutics	Annemieke Aartsma-Rus, Arthur Krieg, Laura Sepp-Lorenzino, Bruce Sullenger
April 14–18	Fundamental Immunology & Its Therapeutic Potential	James Allison, Eric Pamer, Fiona Powrie, Stephen Smale
April 21–25	The Ubiquitin Family	Ronald Hay, Ron Kopito, Cynthia Wolberger
April 28–May 2	Telomeres & Telomerase	Julia Cooper, Titia de Lange, Roger Reddel
May 2–5	Biology of Genomics of Social Insects	Guy Bloch, Juergen Gadau, Amy Toth
May 5–9	The Biology of Genomes	Ewan Birney, Michel Georges, Elaine Mardis, Molly Przeworski
May 12–16	Biology of Cancer: Microenvironment, Metastasis & Therapeutics	Senthil Muthuswamy, Kornelia Polyak, David Tuveson
May 18–23	Retroviruses	Kathleen Boris-Lawrie, David Evans
May 26–31	80th Symposium: 21st Century Genetics - Genes at Work	Terri Grodzicker, David Stewart, Bruce Stillman
July 16–19	Evolution of Sequencing Technology: A Half-Century of Progress	Mark Adams, Nigel Brown, Mila Pollock, Robert Waterston

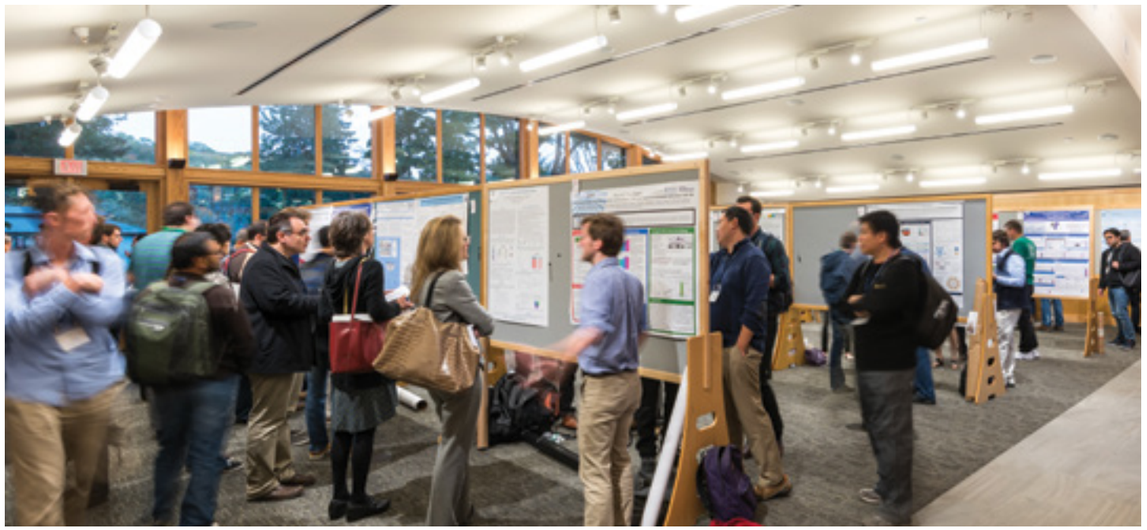
COLD SPRING HARBOR LABORATORY CONFERENCES *(continued)*

	Title	Organizers
August 11–15	Metabolic Signaling & Disease: From Cell to Organism	Daniel Kelly, Mitchell Lazar, Susanne Mandrup
August 18–22	Eukaryotic mRNA Processing	Jean Beggs, Kristen Lynch, Jens Sykke-Andersen
August 25–29	Mechanisms of Eukaryotic Transcription	Patrick Cramer, Katherine Jones, John Lis
September 1–6	Eukaryotic DNA Replication & Genome Maintenance	Anne Donaldson, Anindya Dutta, Johannes Walter
September 8–12	Microbial Pathogenesis & Host Response	Lalita Ramakrishnan, Raphael Valdivia, Malcolm Whiteway
September 15–19	Cell Death	David Andrews, Douglas Green, Anthony Letai
September 24–27	Genome Engineering: The CRISPR/Cas Revolution	Jennifer Doudna, Maria Jasin, Jonathan Weissman
Sept. 29–Oct. 3	Neurobiology of *Drosophila*	Aaron D'Antonio, Diane O'Dowd
October 7–11	Stem Cell Biology	Konrad Hochedlinger, Fiona Watt, Marius Wemig
October 14–17	Probabilistic Modeling in Genomics	Barbara Engelhardt, Thomas Mailund, Adam Siepel
October 28–31	Genome Informatics	Janet Kelso, Daniel MacArthur, Michael Schatz
November 3–7	Cell Biology of Yeasts	Martha Cyert, Daniel Lew, Kenneth Sawin
November 11–15	Single Cell Analysis	Nancy Allbritton, Scott Fraser, Junhyong Kim
November 18–21	Behavior & Neurogenetics of Nonhuman Primates	Nelson Freimer, Jeffrey Rogers
December 2–5	Plant Genomes & Biotechnology: From Genes to Networks	Todd Mockler, Jane Parker
December 9–12	Rat Genomics & Models	Aron Geurts, Michael Gould, Bina Joe, Enrico Petretto

Attendees of 2015 meeting "Wiring the Brain."

COLD SPRING HARBOR LABORATORY COURSES

	Title	Instructors
March 13–16	Workshop on Leadership in Bioscience	Carl Cohen, Dannielle Kennedy
March 30–April 1	The Genome Access Course	Assaf Gordon, Emily Hodges, Gareth Howell, Benjamin King, Jeremy Ward
April 8–21	Protein Purification & Characterization	Albert Courey, James Lee, Sue-Hwa Lin, Michael Marr, Sergei Nechaev
April 8–21	Quantitative Imaging: From Cells to Molecules	Hunter Elliott, Jennifer Waters, Torsten Wittmann
April 9–21	Cell & Developmental Biology of *Xenopus*	Mustafa Khokha, Karen Liu
June 3–16	Single Cell Analysis	James Eberwine, Amy Herr, Michael McConnell
June 3–23	Advanced Bacterial Genetics	Diarmaid Hughes, Beth Lazazzera, Fitnat Yildiz
June 3–23	Mouse Development, Stem Cells & Cancer	Mark Lewandoski, Deneen Wellik
June 3–23	Ion Channels & Synaptic Transmission	Tiago Branco, Stephan Brenowitz, Ian Duguid, Paul Kammermeier
June 4–10	Workshop on Autism Spectrum Disorders	Daniel Geschwind, Sarah Spence
June 18–July 1	Statistical Methods for Functional Genomics	Harmen Bussemaker, Sean Davis, Olivier Elemento, Rafael Irizarry
June 24–30	Workshop on Pancreatic Cancer	Dafna Bar-Sagi, Steven Leach, Anirban Maitraa, David Tuveson
June 26–July 16	*Drosophila* Neurobiology: Genes, Circuits & Behavior	Karla Kaun, Chi-Hon Lee, Stefan Pulver
June 26–July 16	Frontiers & Techniques in Plant Science	Mark Johnson, Shin-Han Shiu, Marja Timmermans
June 30–July 16	Advanced Techniques in Molecular Neuroscience	Cary Lai, Joseph Loturco, Anne Schaefer
July 7–20	Vision: A Platform for Linking Circuits, Perception & Behavior	Farran Briggs, Andrew Huberman
July 14–27	Proteomics	Michelle Cilia, Ileana Cristea, Katalin Medzihradszky, Darryl Pappin
July 21–August 10	Eukaryotic Gene Expression	Karen Adelman, Geeta Narlikar, Ali Shilatifard, Dylan Taatjes
July 21–August 10	Yeast Genetics & Genomics	Grant Brown, Maitreya Dunham, Marc Gartenberg
July 21–August 10	Imaging Structure & Function in the Nervous System	Florin Albeanu, Michael Orger, Lucy Palmer, Philbert Tsai, Jack Waters, Karen Zito
July 23–August 2	Neural Data Science	Mark Reimers, Pascal Wallisch



Nicholls Biondi Hall provides a brilliant new venue for posters and presentations.

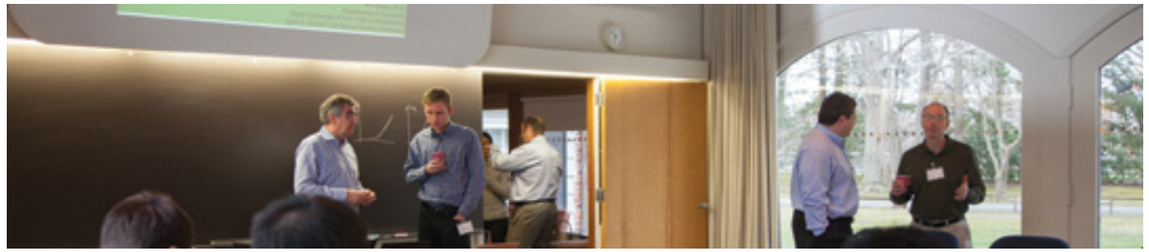
COLD SPRING HARBOR LABORATORY COURSES *(continued)*

	Title	Instructors
July 27–August 10	Synthetic Biology	John Dueber, Mary Dunlop, Karmella Haynes, Julius Lucks, Pamela Peralta-Yahya, Stanley Qi
August 4–10	Cellular Biology of Addiction	Antonello Bonci, Christopher Evans, Brigitte Kieffer
September 2–4	The Genome Access Course (NYGC)	Assaf Gordon, Emily Hodges, Gareth Howell, Benjamin King, Jeremy Ward
October 12–27	X-Ray Methods in Structural Biology	William Furey, Gary Gilliland, Alexander McPherson, James Pflugrath
October 12–27	Programming for Biology	Simon Prochnik, Sofia Robb
Oct. 28–Nov. 3	Computational & Comparative Genomics	Aaron Mackey, William Pearson, Lisa Stubbs
November 9–22	Antibody Engineering & Phage Display	Don Siegel, Gregg Silverman
November 10–22	Advanced Sequencing Technologies & Applications	Elaine Mardis, Gabor Marth, William McCombie, Aaron Quinlan, Michael Schatz
November 16–18	The Genome Access Course	Assaf Gordon, Emily Hodges, Gareth Howell, Benjamin King, Jeremy Ward
December 2–6	Scientific Writing Retreat	Charla Lambert, Stephen Matheson

COLD SPRING HARBOR ASIA CONFERENCES

	Title	Organizers
May 4–8	Precision Cancer Biology & Medicine	Patrick Tan, Cun-Yu Wang, Paul Workman, Qimin Zhan
May 11–15	Membrane Proteins: Structure & Function	Martin Caffrey, Nieng Yan, Ming Zhou
June 1–5	Lipid Metabolism & Human Metabolic Disorders	Pingsheng Liu, (Hongyuan) Rob Yang
June 8–12	Frontiers of Plant Biology: Epigenetics & Development	Xiaofeng Cao, Justin Goodrich, Doris Wagner
June 19–22	International Brain Projects	Maoyen Chi, Joshua Huang, Liqun Luo, David Stewart
June 22–26	Novel Insights into Glia Function & Dysfunction	Shumin Duan, Mengsheng Qiu, Bruce Ransom
June 29–July 3	Francis Crick Symposium: Advances in Neuroscience	Yang Dan, Bai Lu, Botond Roska
September 14–18	Molecular Basis of Aging & Disease	Adam Antebi, Jing-Dong Jackie Han, Brian Kennedy, Jan Vijg
September 21–25	Tumor Immunology & Immunotherapy	Xuetao Cao, Sumiya Dalangood, Olivera Finn, Shimon Sakaguchi, Laurence Zitogel
October 12–16	Mitochondria	Paolo Bernardi, Andrew Dillin, Xiaodong Wang
October 19–22	CSHA/ISSCR Joint Meeting Stem Cells: From Basic Biology to Disease Therapy	Hongkui Deng, Andrew Elefanty, Gordon Keller, Duanqing Pei
October 26–30	Biological Rhythms	Carla Green, Joseph Takahashi, Hiroki Ueda, Han Wang
November 2–6	Bacterial Infection & Host Defense	Kenya Honda, Samuel Miller, Craig Roy, Feng Shao, Jörg Vogel
November 9–13	Targeting Cell Death Mechanisms for the Treatment of Human Diseases	Douglas Green, Jiahuai Han, Domagoj Vucic, Junying Yuan
November 16–20	Development & Pathophysiology of Respiratory Systems	Paul Noble, Min Wu
December 1–4	Joint Meeting of the Molecular Biology Society of Japan & the Japanese Biochemical Society*	
December 2–5	CSHA/AACR Joint Meeting - Big Data, Computation & Systems Biology in Cancer	Andrea Califano, William Hahn, Satoru Miyano, Xuegong Zhang
December 7–11	New Advances in Optical Imaging of Live Cells & Organisms	Guoqiang Bi, Wenbiao Gan, Arthur Konnerth, Akihiro Kusumi

*Adjunct meeting



	Title	Organizer(s)
February 20–25	Boehringer Ingelheim Fonds Fellows Retreat	Sandra Schedler, Claudia Walther
March 9–11	Exercise Science & Health	Russell Pate, Laurie Goodyear, Timothy Church
March 17–20	Brain Rhythms as Potential Targets for Intervention in Cognitive Dysfunction	Roi Cohen Kadosh, Marjorie Garvey, Bettina Osborn, Michele Pearson, Bradley Postle
April 6–9	Biophysical Properties & Biological Significance of Amyloid-β Assemblies	Karen Ashe, Robert Tycko
April 14–17	Creating Patient-Specific Neural Cells for the *In Vitro* Study of Brain Disorders	Fred Gage, Rudolph Jaenisch
April 19–22	Neuronal Response Variability & Correlation	Laurence Abbott, Kanaka Rajan, John Reynolds
April 25–27	Wheat Genomics	Michael Bevan, Mario Caccamo
May 1–3	NIMH Brain Camp VII	Joyce Chung, Thomas Insel
June 14–17	What Really Improves the Lives of People with Schizophrenia	Robert Heinssen, John Kane
June 18–20	Integrated Translational Science Center Workshop	Laurence Baker, Lee Ellis, Edison Liu, Anne Schott, David Tuveson
September 1–4	Mitochondria & Cancer	Navdeep Chandel, David Sabatini
September 15–18	Therapeutic Approaches to Prion Disease & Other Neurodegenerative Conditions	John Collinge, Jeffery Kelly
September 20–22	Therapeutic Use of Ketamine for Treating Severe Depression - Risks & Potential	Hakon Heimer, Rhonda Robinson Beale, Jan Witkoswki,
September 27–30	Therapeutic Development for ALS	Lucie Bruijn, Timothy Miller, Dinah Sah, Clive Svendson
October 4–7	What is Needed to Harness Chemogenetics for the Treatment of Human Brain Disorders?	Gary Aston-Jones, Bryan Roth
October 13–16	HIV-1 & How to Kill a Killer: Attempts at Total or Functional Cure of HIV-1	Steven Deeks, Robert Gallo, Robert Siciliano
October 18–21	Lustgarten Scientific Meeting	David Tuveson
November 1–4	The New Era of Precision Medicine in Epilepsy	Samuel Berkovic, David Goldstein, Erin Heinzen, Daniel Lowenstein
November 11–13	Preventing Inherited BRCA Cancer: A Think Tank for Innovative Strategies, Milestone Objectives & Research Priorities	Thomas Bock, Lawrence Brody
November 15–18	How Can the Genetics & Neurobiology of Borderline Personality Disorder Contribute to Its Diagnosis & Treatment?	Hakon Heimer, Antonia New, John Oldham
December 7–10	Tumor Cell Mechanism: Finding New Targets for Therapeutic Intervention	Lewis Cantley, Steven McKnight

2015 WSBS DOCTORAL RECIPIENTS

	Thesis Advisor	Academic Mentor	Current Position
Colleen Carlston	Christopher Hammell	Hiroyasu Furukawa	Clinical Molecular Genetics Fellow, University of Utah
Silvia Fenoglio	Gregory Hannon	Linda Van Aelst	Postdoctoral Fellow, Massachusetts Institute of Technology
Wee Siong Goh	Gregory Hannon	Hiroyasu Furukawa	Research Fellow, Institute of Molecular and Cellular Biology, Singapore
Jack Walleshauser	Leemor Joshua-Tor	Christopher Hammell	Postdoctoral Fellow, Yale University

Watson School of Biological Sciences 2015 commencement convocation ceremony.

CSHL PRESS PUBLICATIONS

Serials

Genes & Development, Vol. 29 (www.genesdev.org)

Genome Research, Vol. 25 (www.genome.org)

Learning & Memory, Vol. 22 (www.learnmem.org)

RNA, Vol. 21 (www.rnajournal.org)

Cold Spring Harbor Symposia in Quantitative Biology, Vol. 79: *Cognition*, edited by Cori Bargmann, Daphne Bavelier, Terrence Sejnowski, David Stewart, and Bruce Stillman

Cold Spring Harbor Protocols (www.cshprotocols.org)

Cold Spring Harbor Perspectives in Biology (www.cshperspectives.org)

Cold Spring Harbor Perspectives in Medicine (www.perspectivesinmedicine.org)

Laboratory Manuals

Methods in Yeast Genetics and Genomics: A Cold Spring Harbor Laboratory Course Manual, 2015 Edition, by Maitreya J. Dunham, Marc R. Gartenberg, and Grant W. Brown

Cell Death Techniques: A Laboratory Manual, edited by Ricky W. Johnstone and John Silke

Handbooks

The Next-Generation DNA Sequencing Informatics, Second Edition, edited by Stuart M. Brown

Using R at the Bench: Step-by-Step Data Analytics for Biologists, by Martina Bremer and Rebecca W. Doerge

Textbooks

Epigenetics, Second Edition, edited by C. David Allis, Marie-Laure Caparros, Thomas Jenuwein, and Danny Reinberg; Associate Editor Monika Lachlan

Monographs (Topic Collections from *Perspectives in Biology* and *Perspectives in Medicine*)

Retinal Disorders: Genetic Approaches to Diagnosis and Treatment, edited by Eric A. Pierce, Richard H. Masland, and Joan W. Miller

Glia, edited by Ben A. Barres, Marc R. Freeman, and Beth Stevens

Intellectual Property in Molecular Medicine, edited by Salim Mamajiwalla and Rochelle Seide

Mitosis, edited by Mitsuhiro Yanagida, Anthony A. Hyman, and Jonathan Pines

The Hepatitis B and Delta Viruses, edited by Christoph Seeger and Stephen Locarnini

Molecular Approaches to Reproductive and Newborn Medicine, edited by Diana W. Bianchi and Errol R. Norwitz

Size Control in Biology: From Organelles to Organisms, edited by Rebecca Heald, Iswar K. Hariharan, and David B. Wake

Neurogenesis, edited by Fred H. Gage, Gerd Kempermann, and Hongjun Song

DNA Recombination, edited by Stephen Kowalczykowski, Neil Hunter, and Wolf-Dietrich Heyer

Epilepsy: The Biology of a Spectrum Disorder, edited by Gregory L. Holmes and Jeffrey L. Noebels

Learning and Memory, edited by Eric R. Kandel, Yadin Dudai, and Mark R. Mayford

Aging: The Longevity Dividend, edited by S. Jay Olshansky, George M. Martin, and James L. Kirkland

History

The Road to Discovery: A Short History of Cold Spring Harbor Laboratory, by Jan A. Witkowski

Other

Decoding the Language of Genetics, by David Botstein

Orphan: The Quest to Save Children with Rare Genetic Disorders, by Philip R. Reilly

CSHL Annual Report 2014, Yearbook Edition

Banbury Center Annual Report 2014

E-books (Kindle editions)

Epigenetics, Second Edition, edited by C. David Allis, Marie-Laure Caparros, Thomas Jenuwein, and Danny Reinberg; Associate Editor Monika Lachlan

Orphan: The Quest to Save Children with Rare Genetic Disorders, by Philip R. Reilly

Decoding the Language of Genetics, by David Botstein

Methods in Yeast Genetics and Genomics: A Cold Spring Harbor Laboratory Course Manual, 2015 Edition, by Maitreya J. Dunham, Marc R. Gartenberg, and Grant W. Brown

Using R at the Bench: Step-by-Step Data Analytics for Biologists, by Martina Bremer and Rebecca W. Doerge

Aging: The Longevity Dividend, edited by S. Jay Olshansky, George M. Martin, and James L. Kirkland

Experimental Design for Biologists, Second Edition, by David J. Glass

Career Options for Career Options for Biomedical Scientists, edited by Kaaren Janssen and Richard Sever

Audiobook (Audible or iBook editions)

Orphan: The Quest to Save Children with Rare Genetic Disorders, by Philip R. Reilly

Websites

Cold Spring Harbor Monographs Archive Online (www.cshmonographs.org)

Cold Spring Harbor Symposium on Quantitative Biology Archive (symposium.cshlp.org)

Services

bioRxiv, the preprint server for biology (www.bioRxiv.org)

BioSupplyNet, scientific supply directory (www.biosupplynet.com)

FINANCIAL REPORTS

W. Dillaway Ayres, Jr.

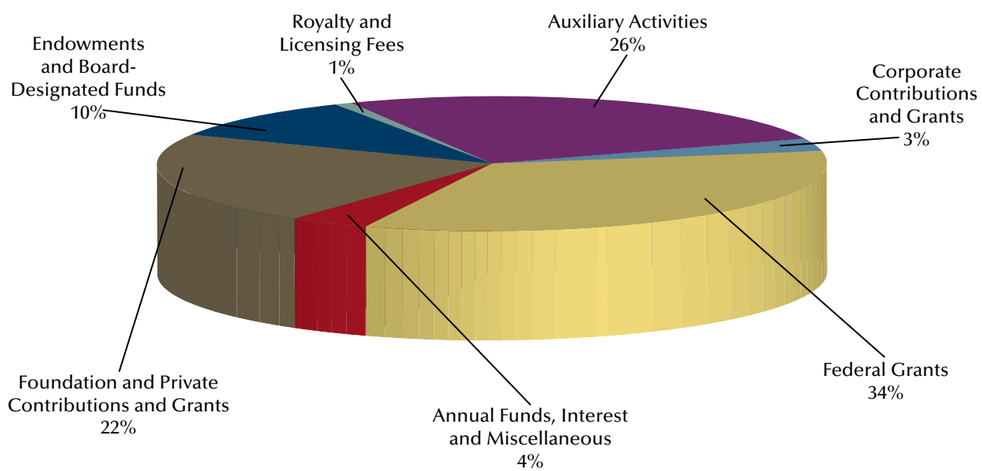
As Bruce Stillman rightly points out in his President's Message, basic discovery science, the heart of Cold Spring Harbor Laboratory's mission, is becoming increasingly expensive. This is a result of many factors including escalation in expenses associated with scientific equipment, supplies, and recruitment 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.

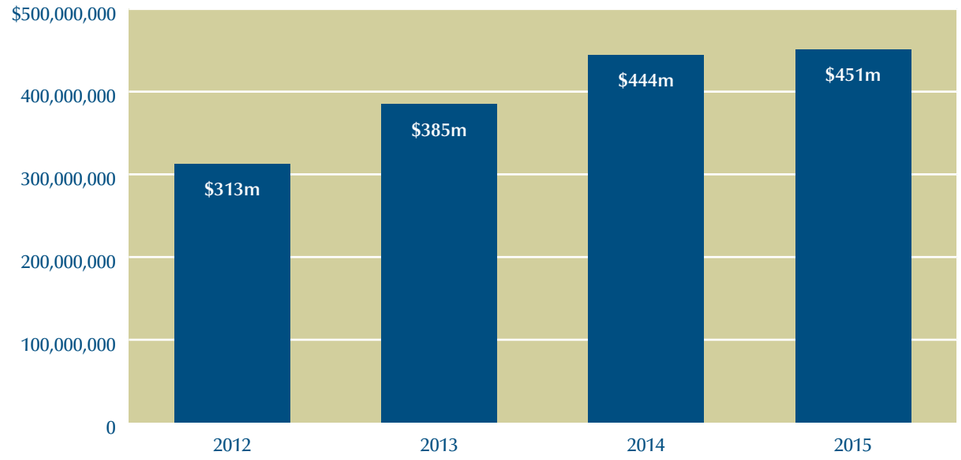
At the same time, the Laboratory has been very successful in attracting funds from private foundations and philanthropy. One need only look at the shift in the mix of our research funding over the last decade. In 2005, federal grants made up nearly 60% of the total, with private sources at 20%. Ten years 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.

2015 CSHL Sources of Revenue



CSHL Endowment Year-End Value and Performance



Performance				
Year	2012	2013	2014	2015
Return	12.4%	16.4%	4.3%	-0.2%

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 endowment 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 anti-science discourse in America. In his words, "I think there is a clear and present danger that the US 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 anti-science 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.

Consolidated Balance Sheet

December 31, 2015

(with comparative financial information as of December 31, 2014)

	2015	2014
Assets:		
Cash and cash equivalents	$ 54,209,176	56,309,959
Grants receivable	9,545,355	10,551,528
Contributions receivable, net	30,100,043	58,786,259
Investments	449,931,993	442,830,529
Investment in employee residences	6,161,403	5,159,378
Restricted use assets	5,412,103	5,127,815
Other assets	10,270,883	9,983,360
Land, buildings, and equipment, net	230,619,980	231,650,890
Total assets	$ 796,250,936	820,399,718
Liabilities and net assets:		
Liabilities:		
Accounts payable and accrued expenses	$ 10,048,146	12,510,995
Deferred revenue	8,004,642	5,509,689
Interest rate swap	34,052,132	33,623,553
Bonds payable	95,608,887	95,542,618
Total liabilities	147,713,807	147,186,855
Net assets:		
Unrestricted	342,262,835	325,723,978
Temporarily restricted	192,160,567	236,314,595
Permanently restricted	114,113,727	111,174,290
Total net assets	648,537,129	673,212,863
Total liabilities and net assets	$ 796,250,936	820,399,718

Consolidated Statement of Activities

Year ended December 31, 2015

(with summarized financial information for the year ended December 31, 2014)

	Unrestricted	Temporarily Restricted	Permanently Restricted	2015 Total	2014 Total
Revenue and other support:					
Public support - contributions and nonfederal grant awards	$ 16,581,343	11,563,092	2,939,437	31,083,872	39,283,518
Federal grant awards	31,750,274	–	–	31,750,274	27,176,257
Indirect cost allowances	27,286,692	–	–	27,286,692	23,710,599
Investment return utilized	17,887,633	–	–	17,887,633	16,497,482
Program fees	8,681,384	–	–	8,681,384	6,896,378
Publications sales	9,737,489	–	–	9,737,489	10,030,061
Dining services	4,819,543	–	–	4,819,543	4,322,717
Rooms and apartments	3,880,805	–	–	3,880,805	3,638,654
Miscellaneous	5,183,130	–	–	5,183,130	6,632,532
Net assets released from restrictions	43,903,946	(43,903,946)	–	–	–
Total revenue and other support	169,712,239	(32,340,854)	2,939,437	140,310,822	138,188,198
Expenses:					
Research	86,078,788	–	–	86,078,788	85,732,121
Educational programs	19,849,038	–	–	19,849,038	17,213,213
Publications	9,152,372	–	–	9,152,372	9,466,527
Banbury Center conferences	1,591,739	–	–	1,591,739	1,486,354
DNA Learning Center programs	2,001,720	–	–	2,001,720	1,973,519
Watson School of Biological Sciences programs	3,246,931	–	–	3,246,931	3,422,312
General and administrative	17,204,666	–	–	17,204,666	16,603,749
Dining services	5,924,858	–	–	5,924,858	5,704,911
Total expenses	145,050,112	–	–	145,050,112	141,602,706
Excess (deficiency) of revenue and other support over (under) expenses	24,662,127	(32,340,854)	2,939,437	(4,739,290)	(3,414,508)
Other changes in net assets:					
Investment return excluding amount utilized	(7,694,691)	(11,813,174)	–	(19,507,865)	(31,486)
Change in fair value of interest rate swap	(428,579)	–	–	(428,579)	(15,010,072)
Increase (decrease) in net assets	16,538,857	(44,154,028)	2,939,437	(24,675,734)	(18,456,066)
Net assets at beginning of year	325,723,978	236,314,595	111,174,290	673,212,863	691,668,929
Net assets at end of year	$ 342,262,835	192,160,567	114,113,727	648,537,129	673,212,863

Consolidated Statement of Cash Flows

Year ended December 31, 2015

(with comparative financial information for the year ended December 31, 2014)

		2015	2014
Cash flows from operating activities:			
Decrease in net assets	$	(24,675,734)	(18,456,066)
Adjustments to reconcile change in net assets to net cash provided by operating activities:			
Change in fair value of interest rate swap		428,579	15,010,072
Depreciation and amortization		13,808,887	13,942,830
Donated equipment		(1,880,032)	–
Amortization of deferred bond costs		66,269	66,269
Net depreciation (appreciation) in fair value of investments		4,238,813	(12,908,048)
Contributions restricted for long-term investment		(3,057,415)	(5,020,506)
Changes in assets and liabilities:			
Grants receivable		1,006,173	(2,045,360)
Contributions receivable, net		25,537,066	48,392,029
Restricted use assets		(284,288)	(623,048)
Other assets		(287,523)	2,357,289
Accounts payable and accrued expenses, net of financing activities		(1,848,350)	959,182
Deferred revenue		2,494,953	299,798
Net cash provided by operating activities		15,547,399	41,974,441
Cash flows from investing activities:			
Capital expenditures		(10,897,945)	(13,605,145)
Proceeds from sales and maturities of investments		44,262,648	75,649,786
Purchases of investments		(55,602,925)	(121,501,780)
Net change in investment in employee residences		(1,002,025)	(810,514)
Net cash used in investing activities		(23,240,247)	(60,267,653)
Cash flows from financing activities:			
Contributions restricted for long-term investment		2,939,438	4,001,838
Contributions restricted for investment in capital		117,977	1,018,668
Decrease in contributions receivable		3,149,150	3,209,572
(Decrease) increase in accounts payable relating to capital expenditures		(614,499)	1,114,499
Net cash provided by financing activities		5,592,066	9,344,577
Net decrease in cash and cash equivalents		(2,100,783)	(8,948,635)
Cash and cash equivalents at beginning of year		56,309,959	65,258,594
Cash and cash equivalents at end of year	$	54,209,176	56,309,959
Supplemental disclosure:			
Interest paid	$	3,978,881	4,013,111

INSTITUTIONAL ADVANCEMENT

INSTITUTIONAL HIGHLIGHTS

For 125 years, CSHL research and education programs have been central to the advancement of biology and genetics. Our Long Island campuses, now spread over nearly 200 acres, have been centers for the global exchange of scientific knowledge. Throughout the decades, the Laboratory has prized its stewardship of life science, with great appreciation for the public and private funds that have propelled us forward.

CSHL supporters are dedicated to seeing the results of research benefit mankind. 2015 was a year replete with examples of how basic scientific research benefits society. In April, CSHL entered into a strategic affiliation with one of the nation's largest health systems, Northwell Health—a unique relationship that will invest more than $120 million in cancer research and bring the Laboratory's science more rapidly toward the clinic. The new partnership underscores the significance of biomedical research to healthcare today.

The importance of CSHL can also be felt in the economy. An economic impact study found that the institution, directly employing 1,100, indirectly accounts for over 500 additional jobs, and annually brings 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 entire study can be found in the About Us section of www.cshl.edu.

Private philanthropy drives a great deal of the most innovative basic research. The Laboratory is grateful to all donors, who allow our science to push beyond the mainstream. In 2015 we celebrated the 10th Double Helix Medals Dinner, raising $4.5 million and honoring Katie Couric, Anne Wojcicki and David Botstein. Thanks to the leadership of our Board of Trustees, this spectacular event put CSHL research in the New York City spotlight. In November, George D. Yancopoulis, M.D., Ph.D., President of Regeneron Laboratories, joined the institution's governing body, bringing his unique perspective as a scientist, clinician, and industry leader. A special thank you to trustees and other benefactors for generous gifts to research programs: Lalit and Kavita Bahl, Jenny and Jeff Kelter, Mary W. Harriman Foundation, Gladys and Roland Harriman Foundation, and Leslie and Stu Weisbrod. Jim and Liz Watson continued their legacy as philanthropic champions of the Laboratory with a major gift toward educational programs.

To celebrate its 125th anniversary, CSHL opened its campus in June to non-scientists—our friends in the community. Faculty, students and employees were out in full force to tour, explain, and share their knowledge with nearly 600 visitors. This event helped inaugurate Nicholls Biondi Hall, built with a gift from CSHL Chairman Jamie C. Nicholls and O. Francis Biondi to host scientific poster sessions for the Meetings & Courses Program.

Throughout the year, we welcomed more than 2000 visitors for tours and public lectures about CSHL research and education developments. We engaged virtual visitors in multimedia experiences about CSHL's past, present and future at www.cshl.edu/125. A special 125th Anniversary series of public lectures featured luminaries in science and society: Dr. Sylvia Earle, National Geographic Explorer in Residence; Peter Neufeld, the Innocence Project; Dr. Michael Wigler, CSHL; Dr. David Tuveson, CSHL and the Lustgarten Foundation; and Dr. Jeremy Farrar, the Wellcome Trust.

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2015 Double Helix honorees Katie Couric, David Botstein and Anne Wojcicki with CSHL President Bruce Stillman.

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2015 Golf honorees Tom and Trudy Calabrese pictured with longtime friend Mary Lindsay.

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Caroline Monti Saladino, President of the Don Monti Memorial Research Foundation, pictured with CSHL scientists at the 2015 Ball of the Year. The Monti Foundation is a longtime supporter of cancer research at CSHL.

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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.

*Deceased

Chris Pendergast and Frank Verdone of Ride for Life presented a $300,000 check to Drs. Molly Hammell and Josh Dubnau to fund research to investigate the genetic causes of ALS.

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Jerry Swartz, Hirsh Cohen, Bill Bialek, Bruce Stillman, Jim Watson and CSHL neuroscientists at the April 1 dedication of the Jerome Swartz Centers for Neuroscience.

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CSHL neighbors host dinner parties for visiting scientists at the annual Dorcas Cummings lecture and symposium.

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Students at the Hotchkiss School held a color run fundraiser in April to support autism research at CSHL.

*Deceased

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To discuss making a gift to CSHL, contact Diane Fagiola at 516-367-8471 or email fagiola@cshl.edu

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Dr. Klessig, a new Helix Society member and former CSHL scientist, is currently a professor at Cornell University's Boyce Thompson Institute.

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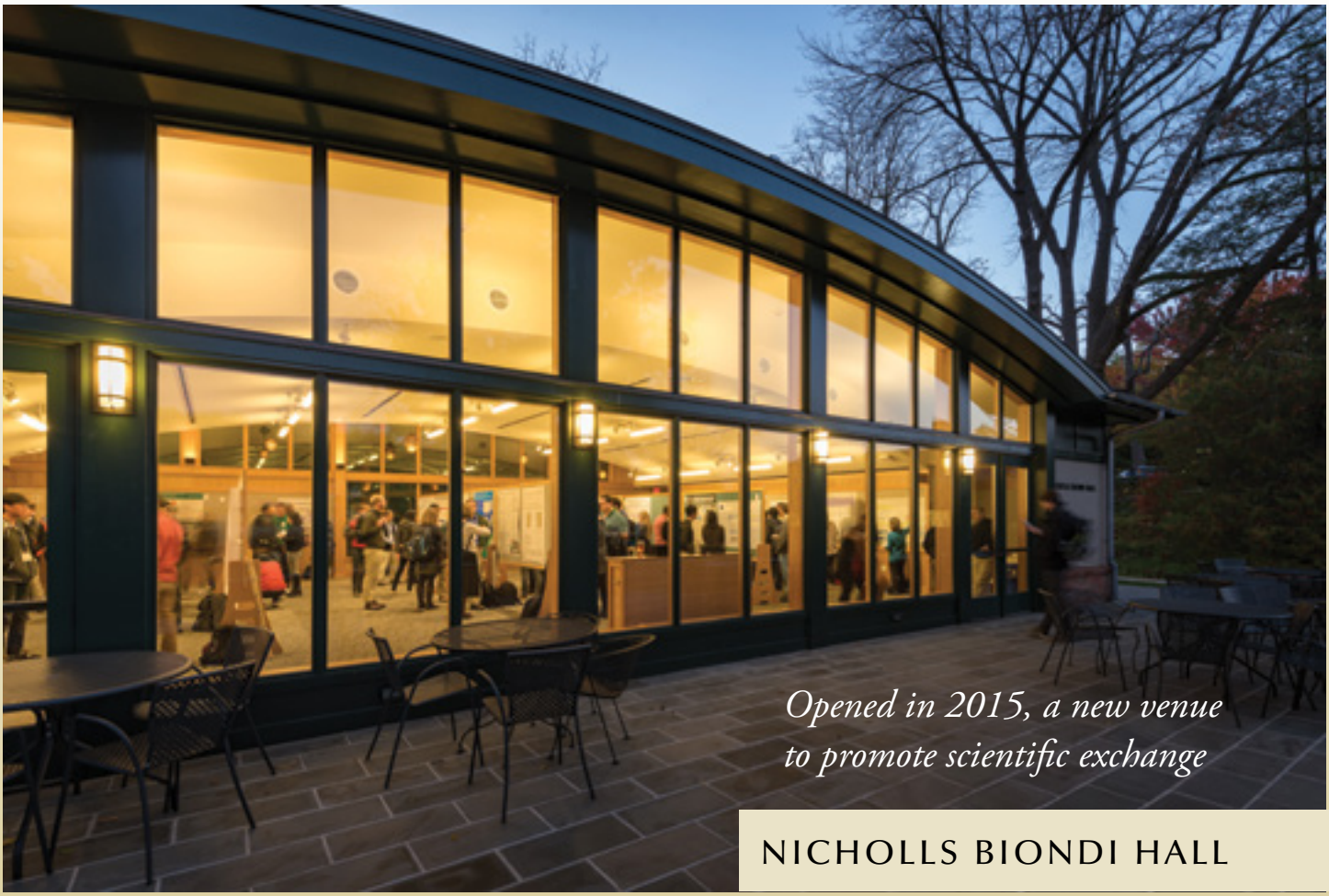

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