Highlights of the Year

Research

In 2016, the hundreds of scientists who work in Cold Spring Harbor Laboratory's 50-plus laboratory groups led or contributed to work disseminated in hundreds of peer-reviewed scientific papers. This research represents the full gamut of CSHL research activity, in Cancer, Neuroscience, Plant Biology, Quantitative Biology, and Genomics. Although it is impossible in a small space to adequately represent the scope of this work, its richness is suggested in the following sample of important findings.

Evidence of Earlier Neanderthal–Modern Human Mating

A. Siepel

We have been aware for some time that Neanderthals and humans mated at some point in their shared past. Initial analysis suggested such contacts occurred some 47,000–65,000 years ago. This year, an international team co-led by Adam Siepel reported an interbreeding event more than 100,000 years ago. This finding, the result of several kinds of advanced computer modeling algorithms comparing complete genomes of hundreds of contemporary humans with complete and partial genomes of four archaic humans, has implications for our knowledge of human migration patterns. The new data, interestingly, shows a signal of breeding in the opposite direction from that already known: bits of human DNA in the genome of a Neanderthal individual. This is in contrast to fragments of Neanderthal DNA in human genomes, which we have known about for years. The team's evidence of "gene flow" from descendants of modern humans into the Neanderthal genome applies to one specific Neanderthal. The modern human sequences in this "Altai Neanderthal" appear to derive from a group of modern human ancestors from Africa that separated early from other humans around the time present-day African populations diverged from one another, about 200,000 years ago.

Insights about NMDA Receptors in Action

H. Furukawa

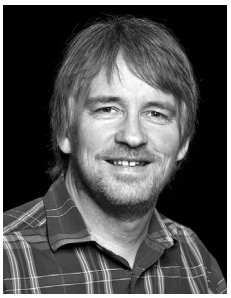
Hiro Furukawa and colleagues continue to make discoveries about the structure of NMDA (*N*-methyl-D-aspartate) receptors in the brain, whose dysfunction is linked to depression, schizophrenia, Alzheimer's, and other illnesses. In two published papers, they shed new light on how the various segments, or domains, of the receptor change shape when the receptor is activated, and how structural differences in variants of specific domains account for differences in how they interact with zinc, an important NMDA regulator. To do this, the team combined two molecular imaging techniques, X-ray crystallography and single-particle electron cryo-microscopy, and observed structures of the receptor in three specific configurations: the activated, nonactive, and inhibited states. Superimposing the crystal structure of the receptor in each of these states revealed which components move—typically by rotating slightly relative to one another—when the ion channel opens, a movement similar to the opening of a camera shutter. They also solved the mystery of why zinc binds much more readily to the "A" variant of the receptor as compared with the "B" form, which is structurally almost identical. Further, they explained why the important candidate drug ifenprodil binds at a site in the "B" form but not in the "A" form. These discoveries will help make receptor-modulating drugs more specific.

Statistical Assessments Underlie Feelings of Confidence

A. Kepecs

Adam Kepecs and his team suggest that the brain is constantly processing data to make statistical assessments that translate into the feeling we call confidence. This feeling of confidence, they assert, is central to decision-making, and, despite ample evidence of human fallibility, the subjective feeling relies on objective calculations, akin to the statistical computations a computer would make. If we did not have the ability to optimally assess confidence, we would routinely find ourselves in a state of indecision, or worse. In experiments with human subjects, Kepecs and colleagues tried to control for different factors that can vary from person to person. The aim was to establish what evidence contributed to each decision. In this way, they could compare people's reports of confidence with the optimal statistical answer. They created video games to compare human and computer performances. Participants rated confidence in each choice they were asked to make on a scale of 1 (a random guess) to 5 (high confidence). They found that human responses were similar to statistical calculations. The brain produces feelings of confidence that inform decisions the same way statistics pulls patterns out of noisy data. It is Kepecs' thesis that statistics—generated by the objective processing of sensory and other data—is the ultimate language of the brain.

New Stem Cell Pathway Points to Higher Staple Crop Yields



D. Jackson

A discovery by David Jackson's team explains how plants regulate the proliferation of their stem cells. This has implications for increasing the yield of maize and other staple crops, perhaps by as much as 50%. The newly discovered regulatory pathway is notable in that it channels signals emanating from a plant's extremities—emerging young leaves called primordia—to the stem cell niche, called the meristem, located at the plant's growing tip. Plant biologists have long known of another pathway, called the CLAVATA-WUSCHEL pathway, that regulates stem cell proliferation from within a portion of the meristem itself, called the organizing center (OC). WUSCHEL is a transcription factor that promotes stem cell proliferation. In the CLAVATA-WUSCHEL pathway, stem cells send back to the OC a negative signal, repressing the signal for proliferation. A similar feedback is established in the newly discovered pathway, although the signal begins in leaves. Having a signal coming from the leaves could act as a kind of environmental sensor, telling totipotent stem cells in the meristem to stop proliferating—a brake, applied from the older, more developed parts of the plant, for example, in response to environmental cues. In maize, the pathway encompassing FEA3—the receptor for the signal from the leaves—and its ligand, FCP1, which the team also discovered, is highly conserved across the plant kingdom. This fact points to the possibility of tweaking the components to achieve significant increases in yield in all the major staple crops.

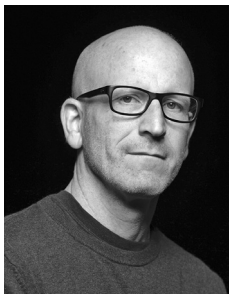
Killing Pancreatic Cancer Cells by Raising Antioxidant Levels

D. Tuveson

Most people have been taught to think that raising antioxidant levels in the body tends to keep cancer at bay. But David Tuveson's lab has demonstrated that in the specific context of pancreatic cells on the road to cancer or already in a malignant state, this is the last thing one wants to do. They find that reducing levels of antioxidants in pancreatic cancer cells can help kill them. More oxidants are being made in malignant cells, but more antioxidants are being made, too, countering the impact of rising oxidation. Without commensurately more antioxidants, malignant cells will die due to excessive oxidation. This suggests a new treatment strategy for the notoriously lethal illness, in which less than 9% of patients survive 5 years. The team focused on a protein called NRF2, a master gene-regulating protein one can tweak to disturb the redox balance in cancer cells. When NRF2 is active, cells synthesize glutathione, an important antioxidant. Can we reduce NRF2 activity or knock it out of action altogether? The team used pancreas organoids to show that when NRF2 is missing, the machinery that translates gene messages into proteins is

very sensitive to fluctuations in oxidant/antioxidant balance. Crucially, protein synthesis was not impacted in normal pancreas cells, indicating an opportunity to capitalize on synthetic lethality—circumstances in which a condition affecting all cells only kills unhealthy ones. The team is now testing various combinations of anticancer agents and glutathione inhibitors in organoid systems with the aim of advancing a novel form of treatment to the clinic.

A Revolutionary Brain-Mapping Method



A. Zador

Anthony Zador and colleagues have published a revolutionary way of mapping the brain at the resolution of individual neurons, which they successfully demonstrated in the mouse brain. Called MAPseq (multiplexed analysis of projections by sequencing), this approach makes it possible in a single experiment to trace the long-range projections of large numbers of individual neurons from a specific region or regions—using much less labor, time, and money than current methods require. MAPseq differs from "bulk tracing" methods now in common use, in which a marker is expressed by neurons and carried along their axons. These markers are good at determining all of the regions where neurons in the source region project to, but they cannot tell scientists that any two neurons in the source region project to the same region, to different regions, or to some of the same regions and some different ones. Zador's technology assigns unique barcode-like identifiers to large numbers of individual neurons via a single injection in any brain region of interest. Each injection consists of a deactivated virus that has been engineered to contain massive pools of individually unique RNA molecules, each of whose sequence—consisting of 30 nucleotides—is taken up by single neurons. The team published a proof-of-concept based on a test of MAPseq showing projections from the locus coeruleus (LC) in the mouse brain. The method will soon be used to map the brains of animals that model various neurodevelopmental and neuropsychiatric illnesses, to see how gene mutations strongly associated with causality alter the structure of brain circuits—and thus, presumably, brain function.

How the Brain Evaluates Results of Our Actions

B. Li

Much of what we do from day to day and even minute to minute is based on our evaluations—our ability to determine whether the consequences of our actions are better or worse than what we expected. But where in the human brain is evaluation performed? How do such evaluations inform our actions? Bo Li's team uncovered a neural circuit that processes evaluations and has succeeded in identifying its sources. They explain how choices are reinforced based on the results of our actions and how we assess those results. The team focused on substructures within the basal ganglia, "nuclei" in the forebrain that include the striatum and the globus pallidus. They discovered that a distinct grouping of neurons within the globus pallidus mediates the evaluation of outcomes. The area containing the set of neurons in the globus pallidus has been named the habenula-projecting globus pallidus, or GPh, which the team discovered is exclusively connected to a tiny structure nearby called the lateral habenula (LHb). In the GPh, information of opposing valence is integrated to determine whether the outcomes of a given action are better or worse than expected. Li's team will now look at the newly traced circuit in mouse models of depression, to see if the circuit as already traced in nondepressed mice is in any way altered.

Long Noncoding RNAs Play a Role in Cancer

Remarkably, only ~2% of the human genome encodes proteins. Nearly 80% of the rest of the genome is transcribed into RNA that does not code for proteins. David Spector and colleagues are learning how some of these RNAs play a role in cancer. They screened thousands of noncoding RNAs to find those expressed at high levels in two types of aggressive breast cancer. When they reduced the level of some of the most overexpressed of these RNAs from mammary tumor

D. Spector

samples, cellular features characteristic of cancer spread were significantly reduced. At first, the team found several hundred long noncoding RNAs (lncRNAs) that were expressed at higher than normal levels in both types of aggressive mouse tumors that they tested. Computational analysis enabled them to prioritize a subset of 30, dubbed mammary-tumor-associated RNAs, or MaTARs. With Ionis Pharmaceuticals, Spector's team designed a series of molecules that bind tightly to, and thereby destroy, specific RNA sequences. They used these antisense molecules to wipe out individual MaTARs in mammary-cancer-derived organoids. They found that individually eliminating 20 of the 30 MaTARs in these organoids diminished features associated with cancer, including cell proliferation, invasion, and migration. The team's next step is to administer antisense molecules to degrade specific MaTARs in mice, in the hope that this will decrease primary tumor mass and/or metastasis.

NETs Deployed by Immune Cells Are Hijacked by Cancers

M. Egeblad

A discovery by Mikala Egeblad and colleagues reveals how neutrophils, the most common type of white blood cell, can be "hijacked" by cancer cells. Using live-imaging technology, her team revealed that a remarkable weapon sometimes deployed by neutrophils against invaders like bacteria can aid metastasis. This astonishing weapon appropriated by cancer cells is a lattice of DNA, ejected from an activated neutrophil upon detection of a threat. These neutrophil extracellular traps or NETs form spider-web-like structures outside the neutrophil. The DNA that forms the backbone of the web is studded with tiny toxic enzymes that can degrade and digest invaders. The team found that cancer cells were able to induce nearby neutrophils to eject their NETs even when no infection or invader was present. Egeblad thinks NETs help aggressive cancer cells by literally eating through the proteins that form a tissue's scaffolding, thus opening up small holes and crevices that cancer cells can occupy. This can be a first step in forming a cancer colony at a site distant from the primary tumor. Working with Dr. Michael Goldberg at the Dana-Farber Cancer Institute, the team hitched the NET-degrading enzyme DNase to nanoparticles and directed these against triple-negative breast cancer in mice, markedly reducing, and for some mice even preventing, metastases to the lung. DNase is already approved for cystic fibrosis patients, so this approach has considerable translational potential.

CRISPR Yields Tomatoes That Flower and Ripen Weeks Earlier

Z. Lippman

Using a simple and powerful genetic method to tweak genes native to two popular varieties of tomato plants, a team led by Zachary Lippman has devised a rapid method to make them flower and produce ripe fruit more than 2 weeks faster than commercial breeders are currently able to do. This means more plantings per growing season and thus higher yield. In this case, it also means that the plant can be grown in latitudes more northerly than currently possible—an important attribute as the earth's climate warms. At the heart of the method are insights obtained by Lippman and colleagues about the evolution of the flowering process in many crops and their wild relatives as it relates to the length of the light period in a day. The hormone florigen and a counteracting "anti-florigen" hormone called SP (for SELF PRUNING) act together, in yin-yang fashion, to, respectively, promote or delay flowering. The team traced a loss of day-length sensitivity in domesticated tomatoes to mutations in a gene called *SP5G* (SELF PRUNING 5G). They discovered that although domesticated plants are insensitive to day length, there remains some residual expression of the antiflorigen *SP5G* gene. They used CRISPR to induce tiny mutations in the *SP5G* gene, inactivating it entirely. When this tweaked

gene was introduced to roma and cherry tomato varieties, the plants flowered earlier, and hence made fruits that ripened earlier. Tweaking another antiflorigen gene that makes tomato plants grow in a dense, compact, shrub-like manner made the early-flowering varieties even more compact and early-yielding. Lippman has thus demonstrated a means of "fast-forward breeding" that could enable growers to expand a plant's geographical range of cultivation, a valuable ability in a period of rapid climate change.

Research Faculty

Awards

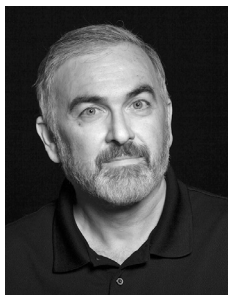
Associate Professor Bo Li and Assistant Professor Je Lee are members of international teams that won the 2016 Human Frontiers Science Program Research Project Grants. Bo's project is "Single-cell resolution imaging and optogenetics in the amygdala fear circuit in behaving animals." Je's project is "Complete cell lineage trees inferred by in situ genotyping of induced somatic mutations."

Professor Adrian Krainer was elected as one of 213 new members of the 236th class of the American Academy of Arts and Sciences. This organization's members include some of the world's most accomplished scholars, scientists, writers, and artists.

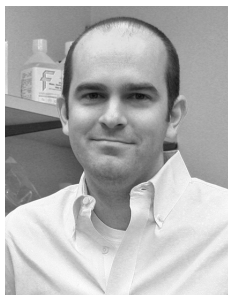
Associate Professor Chris Vakoc, M.D., Ph.D., was awarded the third annual Pershing Square Sohn Prize for Young Investigators in Cancer Research. A finalist in last year's prize, Chris' research employs a novel CRISPR technique that can reveal individual protein domains that sustain cancer cells.

Assistant Professor Camila dos Santos was selected as one of seven 2016 Rita Allen Foundation Scholars. She has found dramatic differences in the pace of breast development between first and second pregnancies, which appear to be mediated by epigenetic mechanisms—molecular changes that affect gene expression without altering DNA sequences. The award will allow the dos Santos lab to assess the relevance of these phenomena for breast cancer risk, which is 30% lower in women who have a full-term pregnancy before the age of 25.

J. Lee



A. Krainer



C. Vakoc

C. dos Santos

Promotions and New Hires

Congratulations to Chris Hammell, who was promoted to Associate Professor. The Laboratory welcomed Ullas Pedmale, Assistant Professor, and Tsung Han Yeh, Research Assistant Professor. Rebecca Leshan, Ph.D., was recruited as the new Director of the Banbury Center. Michael Marchesiello is the new Vice President, Procurement.

CSHL–Northwell Affiliation 2015–2016 Progress

With the goal of bringing basic research insights into the clinic, the CSHL–Northwell Health affiliation links clinicians and scientists. In its second year, the affiliation supported more than 20 new projects at CSHL that have clinical implications. The first joint clinical trial in breast cancer was initiated from research in Nick Tonks' laboratory.

To facilitate future clinical developments, Dr. Robert Maki was named the first Director of the Center for New Cancer Therapies at the Northwell Health Cancer Institute. He holds a joint appointment as CSHL Professor and member of the CSHL National Cancer Institute (NCI)-designated Cancer Center.

The affiliation has launched new education initiatives, including a new research fellow track in clinical medical oncology and laboratory investigation and a new summer research program for Hofstra Northwell School of Medicine students. The first class of

J. Witkowski and R. Leshan

R. Maki

this program trained in the laboratories of David Tuveson, Michael Wigler, Camila dos Santos, and Mickey Atwal.

Half-day retreats held at the Banbury Center have seeded research collaborations between the two institutions. The topics of these meetings have included chronic lymphocytic leukemia and cancers of the prostate, pancreas, brain, breast, and lung.

CSHL Cancer Center

Professor David Tuveson, M.D., Ph.D., was named the new Director of the CSHL Cancer Center. Bruce Stillman held that role for 25 years, and the transition allows him to continue to focus on his long-held role as CSHL President and CEO.

D. Tuveson

Together with the Coalition Against Childhood Cancer (CAC2), CSHL hosted the first-ever "From Bench to Bedside and Beyond" conference convening a wide range of childhood cancer community stakeholders to advance research. Bruce Stillman opened the 2-day program, followed by presentations from Chris Vakoc and Mickey Atwal. Other speakers represented the National Cancer Institute, the nation's top basic and comprehensive cancer centers and the pharmaceutical industry. Other sponsors included Alex's Lemonade Stand Foundation, Bristol-Myers Squibb, United Therapeutics, and Amgen.

CAC2 PEDIATRIC CANCER RESEARCH CONFERENCE 2016

The CAC2 Conference logo

Business Development and Technology Transfer

The ability of CSHL to make game-changing discoveries and apply basic research in developing treatments for disease was demonstrated by FDA approval of the drug Spinraza™ at the end of 2016. This drug, based on the use of antisense oligonucleotide technology that utilizes and a short, RNA-based molecule that targets RNA splicing, is the first effective treatment for the lethal disease called spinal muscular atrophy (SMA). It took more than a decade for Dr. Adrian Krainer and a team of postdocs to understand the fundamental biological process of RNA splicing and convert that knowledge into a drug to counteract the genetic defect in children with SMA.

In 2008, Ionis Pharmaceuticals licensed technology from CSHL based on research conducted in the laboratory of Dr. Krainer, along with his postdoctoral fellow, Dr. Yimin Hua. Ionis

subsequently entered into an agreement with Biogen for development and commercialization of Spinraza™. In 2011, Ionis received FDA permission to begin clinical trials. On December 23, the FDA approved nusinersen, which will be sold by Biogen under the brand name Spinraza™.

The Business Development and Technology Transfer program supports Laboratory scientists interested in working with industry and investors who may need materials or transaction support to enable their research. Andrew Whiteley joined the team as the first CSHL Executive in Residence.

A. Krainer and Y. Hua

In 2016, the program concluded:

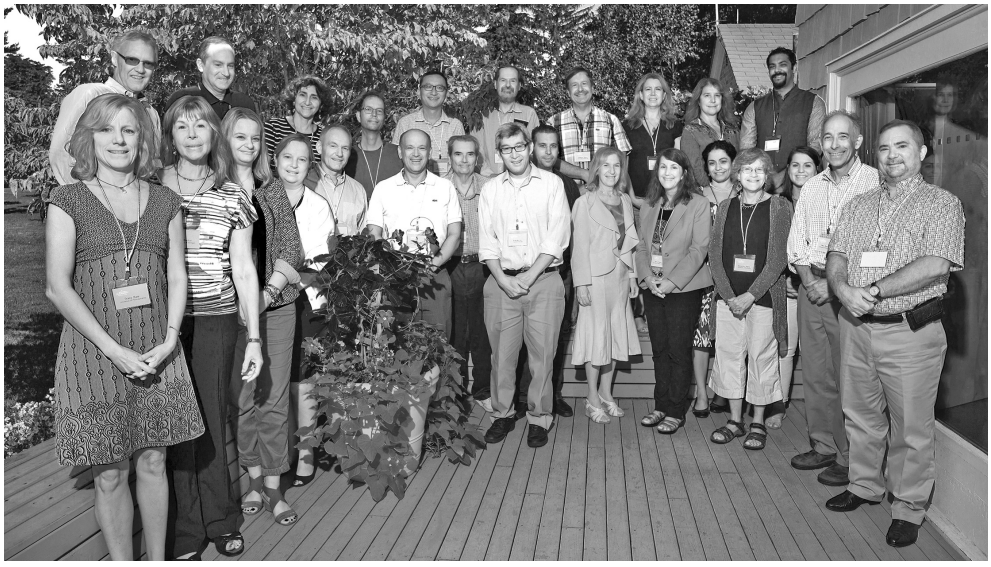
- 10 new license and option agreements
- 11 industry-sponsored research agreements totaling more than $4 million in new funds
- 10 new technology cases
- 18 new patent filings

Education Programs

Banbury Conference Center

The Laboratory's science policy think tank, the Banbury Center, held 42 events, including 20 meetings drawing almost 600 participants. Several meetings were devoted to the topic of mental disorders. One problem that has continued to vex researchers—how to make accurate animal models of such disorders—was the topic of a meeting organized by Dr. Eric Nestler, a leading expert in the field. "Can We Make Animal Models of Human Mental Illness?" considered what behaviors in rodents might be taken as surrogates for behaviors in people.

Another highlight was a meeting devoted to Lyme disease, an example of an emerging infectious disease. Participants at "Diagnostic Tests for Lyme Disease: A Reassessment" made substantial progress in agreeing on next steps toward development of such tests, which are urgently needed.



Participants at Banbury meeting "Can We Make Animal Models of Human Mental Illness?," August 2016

Every year since 1998, a meeting on plant science has been convened at Banbury. This year's meeting focused on "Genomics-Based Accelerated Crop Breeding" and considered the impact of new gene-editing methods such as CRISPR on improving crop performance. Several meetings considered various aspects of cancer research, including possible methods of inhibiting transcription factor STAT-3 and analyzing ways of reducing the toxicity of oxidative chemotherapy.

Topices of focus at this year's meetings included the relationship between DNA science and archaeology and cellular diversity in the mammalian brain, among other subjects. Banbury meetings, which have historically convened diverse groups of experts from many disciplines around a challenge in biological and science policy, are made possible by generous support from individuals, foundations, and corporate sponsors.

Meetings & Courses Program

With roots in the famous Cold Spring Harbor Symposia series, dating to 1933, the scientific conference and advanced technology course program currently includes 55 meetings and 30 to 35 lab and lecture courses held over 2-year cycles. Since 2009, a parallel program of meetings has been held in Suzhou, China, under the aegis of the Cold Spring Harbor Asia (CSHA) program, a wholly owned subsidiary of the Laboratory.

Abstract book for Symposium 81: *Targeting Cancer*

In 2016, the CSHL Meetings attracted 7250 participants to the main campus. The 81st Cold Spring Harbor Symposium focused on Targeting Cancer, reflecting the enormous research progress achieved in recent years. It attracted almost 490 participants, including many of the world's leading cancer researchers. Several new meetings included Transposable Elements and the annual history of molecular biology meeting, which this year addressed HIV/AIDS Research. The program is supported by grants from the National Institutes of Health and the National Science Foundation, as well as the newly invigorated Corporate Sponsor Program.

In its seventh year of operation, the CSHA program held 17 scientific conferences in Suzhou and also arranged meetings on immunology and plant biology in Awaji, Japan, attracting more than 3500 scientists. This program is designed for scientists from the Asia/Pacific region, who make up more than 80% of attendance, and includes symposia, meetings, and Banbury-style discussion meetings. Support comes from a major sustaining grant from the Suzhou Industrial Park.

CSHL's Courses program covers a diverse array of topics in molecular biology, neurobiology, structural studies, and bioinformatics. More than 750 instructors, lecturers, and assistants come

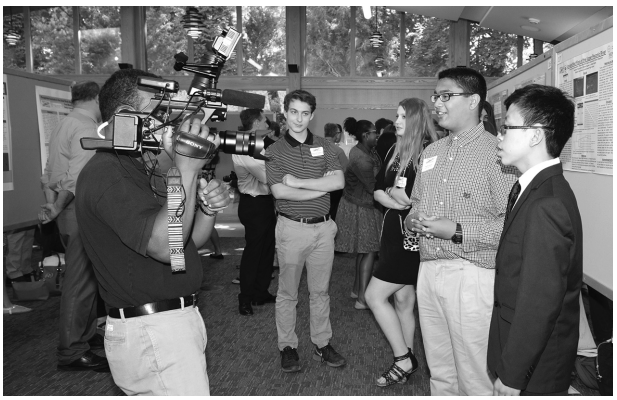
Suzhou meeting

to teach from universities, medical schools, research institutes, and companies around the world. In 2016, about 700 trainees, including advanced graduate students, postdocs, and faculty, attended courses lasting from 1 to 3 weeks.

Courses rely heavily on grants and foundation support, including major support from the Helmsley Charitable Trust, the Howard Hughes Medical Institute, National Institutes of Health, and the National Science Foundation (NSF). Specifically, the Helmsley Interdisciplinary Fellowship Fund provided major funding to 125 scientists to participate in courses outside their primary disciplines. Support from companies in the form of loaned equipment, reagents, and technical expertise is critical to offering participants training at the leading edge.

DNA Learning Center

The DNALC occupies the middle ground on a continuum of the science enterprise that spans from pure research to pure education. It adapts the latest methods and concepts from research to educational settings, empowering students and teachers to participate in real-time research experiences. In the last few years, most of the DNALC's projects funded by grants have focused on scaling research methods to reach larger numbers of students. This effort has expanded our reach from middle and high school students and teachers to undergraduate populations.



Barcode meeting

For the fifth year now, DNA barcoding projects have engaged students in biodiversity studies throughout the New York metropolitan area. Barcode Long Island involved 271 students from 31 schools in Nassau and Suffolk Counties, and the Urban Barcode project involved 214 students from 22 schools in the five boroughs of New York City. These students, mentored by DNALC-trained teachers with easy access to technology resources, investigated lichen biodiversity, ant biodiversity, mislabeling of herbal supplements, invertebrate bio-indicators of habitat health, microbes on smartphones, invasive plants along the Bronx River, and invasive beetles in a Long Island park.

CyVerse (Cyber Universe) is a $100 million NSF project that provides computer infrastructure to solve problems in modern biological research. As educational lead for the project, the DNALC brings students and teachers into the world of biological big data and high-performance computation. Leveraging the CyVerse infrastructure, the DNALC program in RNA sequence analysis allows undergraduate faculty to generate their own data sets of all of the genes active in an organism of their choice. Using bioinformatics tools at the "DNA Subway" created by the DNALC, faculty and students are working together to analyze nearly a trillion nucleotides of sequence data on the XSEDE national supercomputer system. The DNA Subway is the only graphical user interface for XSEDE, which is usually only accessed by experts via command-line programming.

DNA Subway logo

The DNALC is also participating in MaizeCODE, an NSF initiative to develop an encyclopedia of DNA elements that control gene action in corn. Building on CSHL's history of pioneering research on corn and our faculty expertise with the human ENCODE project, MaizeCODE will generate 150 new data sets of RNA and DNA sequence. The DNALC's task is to prepare undergraduate faculty and students to analyze these new data sets as they are released—at the same time and using the same tools as high-level researchers. Surprisingly, the vast majority of the corn genome sequence has not been carefully explored by researchers, so students will be trained to find

elements of gene structure and function that are missed by automated computer analysis. With this project, the DNALC will confirm that good research and education can be exactly the same thing.

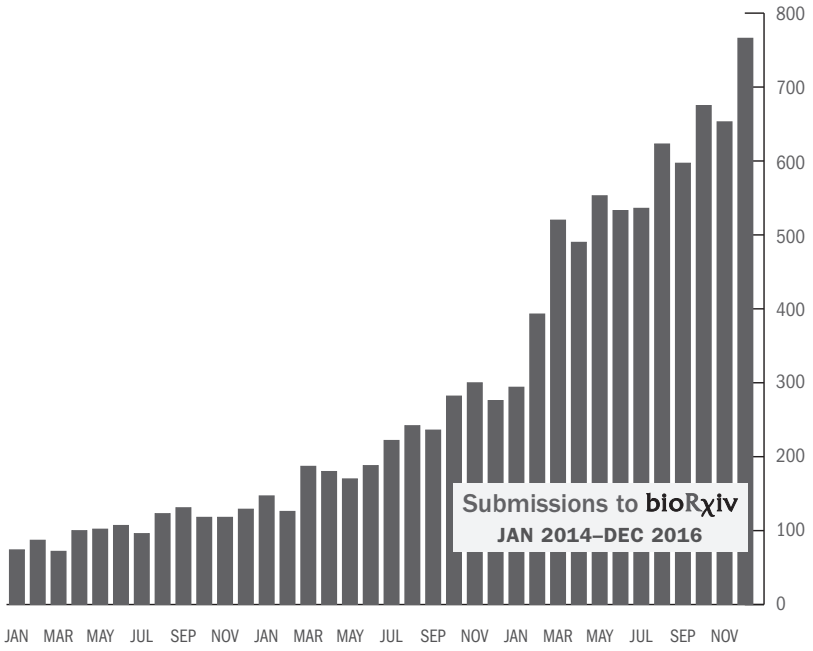
Underpinning these major efforts to bridge research and education are the hands-on laboratory experiences in genetics that the DNALC has historically provided to middle and high school teachers and students. In 2016, 20,884 students attended field trips at our teaching facilities in Cold Spring Harbor, Lake Success, and Harlem. An additional 9100 students received in-school lab instruction by DNALC staff, and 1349 students attended week-long summer camps at various locations across the metro New York area.

Five thousand visitors came to the Dolan DNALC facility for the Ötzi exhibit; 3600 students and members of the general public received guided tours about the 5000-year-old iceman mummy whose life-sized replica calls CSHL home. Monthly *Saturday DNA!* sessions for children and parents drew 171 students and family members. Half of these sessions involved art, with participants "drawing" with glowing microorganisms, creating biodiversity art, and making watercolor "portraits" of cells.

Cold Spring Harbor Laboratory Press

CSHL Press aims to provide scientists worldwide with authoritative, affordable, and appropriate information to further their research and career development. The Press carries forth the Laboratory's commitment to scientific communication.

A highlight this year was the remarkable growth of *bioRxiv*, the Laboratory's open preprint service. *bioRxiv* enables scientists to make draft manuscripts of papers immediately available to the research community and receive feedback before submission to peer-reviewed journals. Manuscript postings in 2016 were 2.5 times higher than in the previous year. With nearly 9000 papers from 40,000 authors in more than 80 countries, *bioRxiv* is now the world's largest source of life science preprints and is accessed more than a million times each month. Established in November 2013, *bioRxiv* has fundamentally changed the communication practices of scientists in biology and ignited similar movements in other sciences. This impact was made



Growth in submissions to *bioRxiv*

possible by the Laboratory's commitment to the founders' vision and by the generosity of Trustee Robert Lourie.

The long-established Press journals *Genome Research* and *Genes & Development* remain preeminent, with editorial teams adept at capturing the new ideas and technologies emerging in a broad range of disciplines. The *RNA* and *Learning & Memory* journals continue serving their specialized research communities in valuable ways. The newer review journals, *CSH Perspectives in Biology, CSH Perspectives in Medicine,* and *CSH Protocols*, continue to advance in stature and financial success. *CSH Molecular Case Studies* had a steady increase in submissions in its first full year and was accepted for indexing by the National Library of Medicine's PubMed service. The Press journals overall had a record yearly download of more than 17 million full-text articles.

The book-publishing program added 13 new titles to its list of 200, including a timely manual on the powerful CRISPR-based technologies. The bundling of print books with electronic editions for tablets, smartphones, and computers was warmly received by busy working scientists. The recent implementation of high-quality print-on-demand delivery for books now means that every title is always available to readers without the burden of costly inventory.

Watson School of Biological Sciences

This year, the Watson School welcomed its 18th incoming class and graduated its 13th. The achievements of the graduate program continued to grow. Students continued to graduate considerably faster than students in comparable Ph.D.-granting institutions and demonstrated an ability to secure excellent jobs. Twenty-two of our graduates have now secured tenure-track faculty positions and are receiving federal grants and publishing papers as independent researchers. Eight have been promoted to Associate Professor. Graduates have also moved into influential positions in administration, publishing, consulting, and industry.

At the 2016 graduation ceremony, seven Ph.D. degrees were awarded, bringing the total since the school's inception to 90. During the year, scientific papers published by students of the school appeared in major journals, bringing the cumulative total to more than 350. Current and former students won prestigious and highly competitive scholarships and fellowships.

2016 WSBS graduation ceremony

In August, the WSBS welcomed 11 new students. Members of the Class of 2016 were selected from 300 applicants.

This year, 1087 undergraduates from around the world submitted applications for 25 slots in the 10-week summer program to conduct advanced research in the laboratory of a CSHL faculty member. This Undergraduate Research Program, along with the equally innovative Partners for the Future Program that brings local high school students into our laboratories during their senior year, provides aspiring scientists with intellectual and social insights into life as a scientist.

125th Anniversary Capital Campaign

Led by Chairman Jamie C. Nicholls, the CSHL Board of Trustees set a goal: to match the institution's scientific preeminence with the financial resources to pursue pioneering research, regardless of the federal funding environment. The goal was achieved as the multi-year 125th Anniversary Capital Campaign closed in 2016, having raised $278 million—ahead of the $250 million goal. During the campaign period, an additional $180 million was donated to ongoing research and education programs—funds not counted toward the Campaign goals. Beginning with Charles Robertson's gift of the first CSHL endowment funds more than 50 years ago, philanthropy continues to be a key driver of discovery at the Laboratory.

The Capital Campaign, guided by the Board Development Committee and chaired by CSHL Trustee Marilyn Simons, focused on raising unrestricted endowment funds to support new research initiatives. A President's Fund of $136 million now provides flexibility to back basic discovery science and the development of new technologies that will have broad impact in many areas of science, agriculture, and health. The Campaign also supports CSHL's world-class Cancer Center, enabling renovation of the Demerec Laboratory and a new initiative linking development of cancer to nutrition and metabolism.

Campaign funds will support expansion of our world-renowned DNA Learning Center in New York City. An initial gift from trustee Laurie Landeau, V.M.D., generated donations of $25 million to bring hands-on lab experiences to public and private schools across the city. Thank you to all who supported the Campaign.

Demerec 3D rendering draft

Double Helix honorees Alan Alda and Roy Vagelos with CSHL President Bruce Stillman and Lesley Stahl

E. Witkin

Trustees

Douglas Schloss was elected to the Board of Trustees. Since 1994, Mr. Schloss has been CEO & Managing Member of Rexford Management. He previously managed arbitrage and investment activities at Marcus Schloss & Co. Mr. Schloss is a graduate of Princeton University and Harvard Business School.

Development

The 11th Double Helix Medals, hosted by Lesley Stahl, honored Alan Alda and Dr. P. Roy Vagelos and raised $4.3 million. The Women's Partnership for Science luncheon, honoring CSHL alumna and Lasker Prize winner Dr. Evelyn Witkin, raised $200,000. Led by the Cold Spring Harbor Laboratory Association, the Annual Fund contributed $7 million, with planned giving by the Helix Society playing a vital role.

Infrastructure

The major renovation of the Firehouse apartments marked the start of a long-term institutional project modernizing student, postdoc, and faculty housing units.

The Laboratory was confronted this year with the failure of the main seawall, originally constructed circa 1830. A temporary repair was effected this year, with its complete replacement planned for the near future.

CSHL seawall

A major chiller plant servicing four research buildings was replaced, increasing cooling capacity to these buildings as well as producing a net cost savings to the Laboratory of $1 million over the next decade. This was the first of a number of projects to modernize the Laboratory's physical plant infrastructure, providing greater reliability, lower operating costs, and the capacity to accommodate the future expansion of research facilities.

Public walking tour of main campus

Community Outreach

The Public Affairs Department works closely with faculty, students, and employees across the Lab to create opportunities for the public to engage with the institution. We offer the surrounding community opportunities to interact and experience CSHL in person through public lectures and talks, tours, concerts, and other special events on and off campus.

In 2016, 19 graduate students and postdocs who serve as expert guides for public walking tours helped acquaint more than 1300 visitors with the Laboratory's history and current pursuits. CSHL is also very well known by the local community's first graders who attend neighborhood public and private schools. More than 130 first graders participated in a hands-on science fair conceived, planned, and led by Watson School graduate students and DNA Learning Center instructors.

Twenty-four hours a day the Internet and social media channels allow CSHL to reach audiences outside of its immediate geography! Stories about the Laboratory's science, scientists, and educators come alive through multimedia products including video, interactive storytelling, and CSHL's own podcast, "Base Pairs." Please visit www.cshl.edu.

CSHL Public Lectures

March 24: David Micklos, Founder and Executive Director of CSHL's DNA Learning Center: *Asking the Wrong Questions about American Science Education*.

May 11: Chris Vakoc, M.D., Ph.D., Associate Professor, Cold Spring Harbor Laboratory: *Cocktails and Chromosomes*.

June 26: Jeremy Farrar, M.D., Infectious Disease Expert & Director of the Wellcome Trust: *Future of Global Health*. This was canceled because of Brexit.

July 6: Nicholas Tonks, Ph.D., F.R.S., Professor, Cold Spring Harbor Laboratory: *Drugging an Undruggable Target: A Scientific Journey from Discovery Research to a Clinical Trial.* This was cosponsored by CSHL, U.S. Trust–Bank of America, Northwell Health, and St. Johnland Nursing Center.

August 4: Zachary Lippman, Ph.D., Associate Professor, Cold Spring Harbor Laboratory: *Cocktails and Chromosomes*.

September 18: Raymond Dattwyler, M.D., Professor of Microbiology/Immunology and Medicine, School of Medicine of New York Medical College; **John Branda, M.D.**, Associate Director

Zador public lecture

of Clinical Microbiology Laboratories, Massachusetts General Hospital, Assistant Professor of Pathology, Harvard Medical School: *Update on Lyme Disease*.

October 16: Jon Cohen, Journalist; **Staffan Hildebrand**, Filmmaker; **Victoria Harden, Ph.D.**, Science historian: *HIV/AIDS Research: Its History and Future*. This was the public session of the 2016 CSHL/Genentech Center Conference on the History of Molecular Biology & Biotechnology.

October 17: Anthony Zador, M.D., Ph.D., Professor, Cold Spring Harbor Laboratory: *Can We Upload Our Mind to the Cloud?*

November 6: Philip R. Reilly, M.D., J.D., Author, geneticist, and former president of the American Society of Law, Medicine and Ethics: *EUGENICS: A Historical Perspective*. This was a 2016 Lorraine Grace lectureship on societal issues of biomedical research.

November 9: Molly Hammell, Ph.D., Assistant Professor, Cold Spring Harbor Laboratory: *Cocktails and Chromosomes*.

CSHL Public Concerts

March 18: Fei Fei Dong, piano
April 21: Stephen Waarts, violin
April 29: Claire Huangci, piano
May 20: Xun Wang, piano
August 26: Southampton Arts Festival Chamber Orchestra
September 9: Sang-Eun Lee, cello
September 16: Drew Petersen, piano
September 29: The Lysander Trio

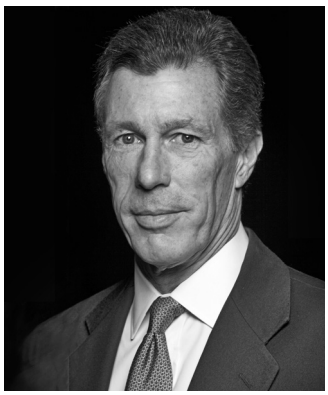
The Lysander Trio

Looking Forward

Thank you to the entire CSHL community for making 2016 such a successful year for our institution. I look forward to a future of CSHL breakthroughs in research and education that will undoubtedly change the world for the better.

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

CHIEF OPERATING OFFICER'S REPORT



Cold Spring Harbor Laboratory enjoyed another positive year of operations. Revenues from federal and private grants, fund-raising, and internal operations were strong. Our endowment funds continued to grow and operating expenses were well controlled.

At year-end, we celebrated the success of our "125th Anniversary Capital Campaign," having exceeded our $250 million goal by nearly $30 million. Of the total funds raised, $186 million was earmarked for endowment. The campaign was effectively and energetically chaired by trustee Marilyn Simons, to whom we owe enormous gratitude, as we do to all of our trustees, who, as a group, contributed 65% of the total. At the same time, our 2016 Annual Fund added $7 million in unrestricted funds. This level of fund-raising is remarkable given the small size of our Development Office and the fact that the Laboratory's constituencies do not include undergraduate alumni or grateful patients.

The Laboratory's research investigators again achieved extraordinary success rates with federal grant awards leading to a 3% increase in federal funding year over year. The ongoing ability to secure a larger slice of a shrinking federal pie speaks to the excellence of the Laboratory's science. This, combined with substantial private support, allows the core basic research to move forward unencumbered. We are enthusiastic as well about our research/clinical collaboration with Northwell Health, which is supporting work that holds the promise of benefiting patients in the clinic.

Cold Spring Harbor's educational divisions are a critical component of the Laboratory's portfolio and major drivers of our international reputation and brand. They include the CSHL Meetings & Courses Program, the Banbury Center, the CSHL Press, the DNA Learning Center, and the Watson School of Biological Sciences. These activities are either self-sustaining or fully funded by endowment and/or philanthropic support. Most importantly, they reinforce the Laboratory's well-established reputation for scientific excellence around the world.

Particularly in an uncertain funding environment, endowment funds are the key to securing the Laboratory's future as a leading and enduring independent institution. It is for this reason that the recently completed fund-raising campaign placed such emphasis on endowment. Fortunately, our fund-raising success, in combination with steady investment returns, has resulted in healthy growth. Since the 2008 financial crisis, our total endowment fund has grown from $218 million to $470 million at year-end 2016. Interestingly, over the 8-year period, we realized $186 million in investment returns and received $188 million in endowment gifts for a total increase of $374 million. At the same time, we spent $122 million of the funds to support research and operations. Despite the growth, we recognize that capital market conditions make it increasingly difficult to expect investment returns that are substantially in excess of the current spending rate plus inflation. Consequently, the decision was made in 2016 to lower our annual spending rate on the endowment from 5% to 4.5%. Although this created an immediate $2 million reduction in available funds this year, the Laboratory was able to successfully absorb the shortfall. We are committed to holding to the 4.5% spending rate in 2017 as well.

All of this bodes well for the Laboratory's intellectual and financial strength going forward. However, we would be ill-advised to become complacent. The headwinds facing academic research in America have been well documented. Political polarization prevents the Congress from passing budgets—forcing the government to operate under "continuing resolutions." This has caused a 20% inflation-adjusted decline in the budget of the National Institutes of Health (NIH)—a primary source of funding for the country's outstanding research institutes, universities, and medical

schools. On top of this, the new administration has proposed a budget with an unprecedented 18% real-dollar cut to the NIH—a reduction that, if implemented, would be a game changer. As Nobel laureate Harold Varmus, a former Director of both the NIH and the National Cancer Institute, articulated in a recent *New York Times* Op-Ed piece, "A substantial NIH budget cut would undermine the fiscal stability of universities and medical schools, many of which depend on NIH funding; it would erode America's leadership in medical research; and it would diminish opportunities to discover new ways to prevent and treat diseases."

It would be a shame were the academic research community to face a challenge of this magnitude at a time of such great progress and promise.

W. Dillaway Ayres, Jr.
Chief Operating Officer

Long-Term Service

Back row (*left to right*): Patricia Wendel, Christopher Oravitz, David Spector, and Bruce Stillman; *center row* (*left to right*): Constance Hallaran, Michael Regulski, James Watson, and Frank Russo; *front row* (*left to right*): Susan Lauter, Christopher Hubert, Philip Renna, Maureen Morrow, and Lorraine McInerny.

The following employees celebrated milestone anniversaries in 2016:

40 years	Patricia Wendel
35 years	Terrance Chisum, Philip Renna
30 years	Christopher Hubert, Adrian Krainer, Susan Lauter, Vincent Meschan, Timothy Mulligan
25 years	Kathleen Cirone, Patricia McAdams, Christopher Oravitz, Michael Regulski, Frank Russo, Linda Van Aelst, Barbara Zane
20 years	William Carmona, Wendy Crowley, Constance Hallaran, Melissa Kramer, Oscar Lastra, Lorraine McInerny, Maureen Morrow, Marcie Siconolfi

Back row (*left to right*): Jerry Armstrong, David Spector, Dill Ayres and Bruce Stillman; *center row* (*left to right*): Andres Alarcon, Cesar Sisalima, Damian Desiderio, Erick Greene, Heather Cosel-Pieper, Louis Malfi, Joseph Carrieri, Bibiane Garite, and Stephanie Muller; *front row* (*left to right*): Hong Jie Shen, Amy Qiu Ji, Gail Sherman, Umamaheswari Ramu, Diane Fagiola, and Stephen Hearn.

15 years — Andres Alarcon, Jerry Armstrong, Edward Anderson, Joseph Carrieri, Maoyen Chi, Heather Cosel-Pieper, Damian Desiderio, Diane Errico, Diane Fagiola, Karen Filasky, Bibiane Garite, Erick Greene, Stephen Gregorovic, Stephen Hearn, Andriana Hincapie, Amy Qiu Ji, Louis Malfi, Alea Mills, Stephanie Muller, Umamaheswari Ramu, Hong Jie Shen, Gail Sherman, Cesar Sisalima, Doreen Ware