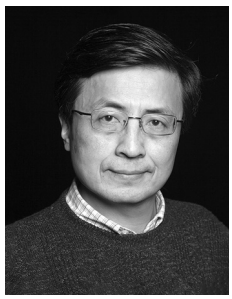
# Highlights of the Year

## Research

More than 600 scientists working in Cold Spring Harbor Laboratory's 50-plus laboratory groups contributed to research that in 2017 was published in the world's major research journals. Their efforts reflect the full spectrum of CSHL's scientific activity in Cancer, Neuroscience, Plant Biology, Quantitative Biology, and Genomics. It is impossible in a small space to adequately represent the scope of this work. The following is a sampling of important findings.

### *Neuronal Types Are Defined by Genes that Shape Their Communication Patterns*



J. Huang

Scientists led by Josh Huang have published an important discovery about the molecular-genetic basis of neuronal cell types. Neurons are the basic building blocks that wire up brain circuits supporting mental activities and behavior. The study, which involves sophisticated computational analysis of the messages transcribed from genes that are active in a neuron, points to patterns of cell-to-cell communication as the core feature that makes possible rigorous distinctions among neuron types across the mouse brain.

The team likens their discovery to the way communication styles and patterns enable people to learn important, definitive things about others; to a significant degree, we are defined by the circle of people with whom we communicate. Using six genetically identifiable types of cortical inhibitory neurons that all release the neurotransmitter GABA, the team sought to discover factors capable of distinguishing the core molecular features of the neurons. Using a high-resolution RNA-sequencing method to identify genes that are expressed in individual neurons, coupled with computational analysis tools developed by Jesse Gillis' group, the team searched for families of genes whose activity exhibited characteristic patterns in each neuron type.

Out of more than 600 gene families, the team found about 40 families whose activity patterns could be used to distinguish the six groups of cells. Surprisingly, Huang says, these cell-defining features fell into just six functional categories of gene families, all of which are vital for cell-to-cell communications. The findings should help scientists sort out the bewildering array of neurons that are intertwined in the brain and come up with a code for how they connect and interact.

### *Dopamine Neurons Factor Ambiguity into Predictions We Depend on*

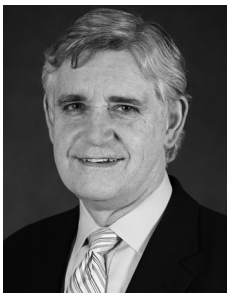
A. Kepecs

Our evolutionary success depends upon our ability to learn and adapt to new conditions, especially when they are changing rapidly. But to make winning decisions, we cannot rely on hardwired instructions. Our success depends on our ability to learn from both successes and failures. Adam Kepecs and his team have been studying how the brain learns, and in recent research, learning how the brain operates in situations where the incoming information is ambiguous.

How does the brain make decisions when the inputs are uncertain? Dopamine-releasing neurons are involved in producing critical teaching signals for the brain, somehow weighing ambiguity—perhaps by reviewing how successfully past experiences guided a new decision. Kepecs' team concludes that dopamine neurons compare predicted outcomes to actual outcomes and send the discrepancy between these as an "error feedback" to many other parts of the brain. This kind of reinforcement learning has been incorporated into many types of artificial intelligence.

The team's research shows that this process in neurons is more complex than previously thought. Their revised model, based on mathematical insight, generates an estimate of the probability that a given choice is correct. Kepecs calls this a measure of the degree of confidence about the decision—in essence, a prediction of accuracy.

### *New Images of ORC Complex Help Solve Three Biological Mysteries*



B. Stillman

L. Joshua-Tor

A ring-shaped protein complex called ORC, or origin recognition complex, performs the first step in the precisely choreographed genome-replication dance that ensures that before cells divide, the genome is duplicated by DNA replication once and only once. Discovered by Bruce Stillman and colleagues in 1991, ORC continues to fascinate scientists, partly because of its multiple functions in the cells and partly because of the difficulty in obtaining images of it at atomic resolution.

Using X-ray crystallography and cryo-EM (electron microscopy), a team led by Leemor Joshua-Tor, in collaboration with Stillman, this year obtained images of human ORC in its active mode at unprecedented resolution. ORC complexes self-assemble in the cell nucleus and bind at specific spots called start sites or origins along the DNA double helix. In human cells, ORC assembles at thousands of origin sites across the entire genome to form an initial configuration called the pre-replication complex, or pre-RC. Each complex requires fuel, which is supplied by adenosine triphosphate (ATP).

In ORC's active phase, the researchers showed that a subassembly containing five ORC subunits engages multiple ATP molecules and forms a partial ring-shaped complex. ATP is also used to recruit another protein component called CDC6, transforming the open ring into a closed ring. By this time, the multipart assembly has engaged and bound to the DNA double helix, which passes through the center of the ring like a bolt through the center of a nut.

The new images help resolve three outstanding mysteries: how DNA binds with ORC, how the ATP fuel is used, and how mutations in ORC complex proteins give rise to a human disorder called Meier–Gorlin syndrome.

### *Using CRISPR Scissors to Vary Traits in Tomato*

Z. Lippman

Zach Lippman and colleagues have used CRISPR-Cas9 technology to rapidly generate variants of the tomato plant that display a broad continuum of three separate, agriculturally important traits: fruit size, branching architecture, and overall plant shape. All are major components in determining how much a plant will yield. The method is designed to work in all food, feed, and fuel crops, including staples like rice, maize, sorghum, and wheat.

Using CRISPR to create different sets of mutations in a gene promoter called SICLV3 (and in several other promoters), the team was able to introduce a wide range of variations in the number of floral organs and locules (gelatinous seed compartments) in tomato plants. The effect is analogous to turning a dimmer switch to vary light levels over a continuous range. In this instance, as the gene's activity declines, the number of flower petals increases, as does the number of seed compartments in the resulting fruit—and, hence, fruit size increases.

All of these effects can be traced to changes in stem cell number in the plant's stem cell reservoir, called the meristem. Traditional genetic breeding involves great time and effort to adapt beneficial variants of relevant genes to the best varieties, which must continuously be improved every year.

The new approach bypasses this constraint by directly generating, and selecting for, the most desirable variants controlling gene activity in the context of other natural mutations that benefit the quality and quantity of fruit in plants.

### *A Defender of the Genome When It Is Naked*

Our genomes are minefields, studded with potentially damaging DNA sequences over which hundreds of thousands of sentries stand guard. Called epigenetic marks, these sentries attach to the double helix at such spots and prevent the underlying DNA sequences from springing into

destructive action. About half the human genome is composed of these damaging sequences. They are where ancient viruses and parasitic elements called transposons and retrotransposons have incorporated themselves over the long course of evolution. These genetic elements need to be kept silent to maintain integrity of the genome.

R. Martienssen

It's astonishing, then, to consider that during two of the most crucial processes in the life cycle, the sentries are removed, leaving the genome naked. The defenders are quickly restored, but only after an interval in which the epigenetic slate is wiped clean. The short period when the genome is naked of the epigenetic marks allows the new embryo to reset and gain its own character, different from the marks that were inherited on the chromosomes from the parents. A team led by Rob Martienssen has now uncovered the existence of what might be considered emergency replacements for the sentries—troops pressed into service across the genome only during these curiously undefended moments.

These defenders are protecting the genome in mammalian embryos, at the very early stages of development before the embryos are implanted in the wall of the maternal uterus. The newly identified defenders are RNA fragments 18 and 22 nucleotides in length. These fragments are perfect complements of sequences in retrotransposons that must be engaged in order for the genomic parasites to be activated.

Martienssen's team thinks the cell is deliberately chopping up full-length transfer RNAs (tRNAs) into smaller fragments precisely because both tRNAs and the fragments cut from them recognize a binding site on retrotransposons that is essential for them to become active. This means the small, tRNA-derived fragments would be able to occupy that site and inhibit retrotransposon replication and mobility, thereby protecting the genome while it is being reset with the new epigenetic marks. This could be one way the genomes of mammals have tolerated vast numbers of transposons and other parasitic elements.

### *The First Cell-Type Census of Mouse Brains*

P. Osten

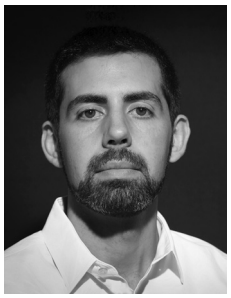
A team led by Pavel Osten has mobilized advanced imaging and computational methods to comprehensively map, or "count," the total populations of specific types of cells throughout the mouse brain. Their "qBrain" (quantitative brain) demonstration revealed that contrary to expectations, the numbers and ratios of three major inhibitory cell types vary in a stereotypical way across different parts of the mouse cortex.

This implies that different cortical areas—for instance, those involving cognition versus those involving perception of sensory stimuli—have evolved to tailor their local circuits to specific brain functions. It is also surprising that although male and female brains did not differ in cell counts in cortical regions, the study identified 11 subcortical areas with sex-specific differences. Strikingly, despite the overall tendency for male brains to be larger, 10 of these regions had more modulatory neurons in females than in males. This shows that, in most respects, there are more cells that modulate signals and exert temporal control in areas regulating reproductive, social, and parenting behaviors in females than in males.

qBrain is built on an automated technology platform that will be used to perform similar analyses of other mammalian brains, from prairie voles to marmoset monkeys and humans. This will enable unprecedented cross-species comparisons.

### *A More Complex Relation between Chromosome Imbalance and Cancer*

More than a century ago, a German-born scientist, Theodor Boveri, reasoned that having the wrong number of chromosomes could cause cells to grow uncontrollably and become the seeds of cancerous tumors. We now know that 90% of solid tumors and 75% of blood cancers have aneuploidy, or abnormal chromosome numbers. But new research from Jason Sheltzer's group suggests that the relationship between aneuploidy and cancer is more complex than previously believed.



J. Sheltzer

They discovered that cells with a single extra chromosome that had been primed to become cancerous actually grew more slowly and formed smaller tumors than similarly primed cells with normal chromosome counts. After a period of weeks, however, the slower growers experienced explosions of growth and displayed pronounced genetic instability.

Sheltzer suspects they rapidly evolved new genomic mutations that enhanced their ability to survive with an extra chromosome. Such rapid evolution in premalignant cells may account not only for their cancerous transformation, but it may also help explain characteristics seen in metastatic cancer cells such as gaining the ability to move to new locations in the body and to resist toxic chemotherapy.

### *A Missing Protein that Can Drive Prostate Cancer Progression*

L. Trotman

A protein called PTEN is one of the body's tumor suppressors. Mutations in the gene encoding it are commonly found in many different types of cancer. Yet some cancer patients show low levels of the PTEN protein even though their *PTEN* genes are normal. Lloyd Trotman and colleagues have discovered that this may be due to defects in a protein called Importin-11, which transports PTEN into the cell nucleus, sheltering PTEN from proteins in the cytoplasm that would otherwise target it for degradation.

Specifically, they demonstrated that loss of Importin-11 may destabilize PTEN, leading to the development of lung, prostate, and other cancers. Mutations in the gene encoding Importin-11 have been identified in human cancers, and Trotman and colleagues found that tumors from lung cancer patients lacking Importin-11 tended to show low PTEN levels as well. The researchers estimate that loss of Importin-11 may account for the loss of PTEN in approximately one-third of lung cancer patients lacking this key anticancer protein.

In prostate cancer, loss of Importin-11 predicted disease relapse and metastasis in patients who had their prostate removed. Trotman's results suggest that Importin-11 is the "Achilles' heel" of the protein-based machinery called the ubiquitination system, which maintains the correct levels of PTEN inside cells.

### *Fibroblast Varieties May Help Explain Why Pancreatic Cancer Is So Hard to Treat*

D. Tuveson

Why are pancreatic tumors so resistant to treatment? One reason is that the wound-like tissue surrounding tumors, called stroma, is much more dense than stromal tissue surrounding other, more treatable tumor types. Stromal tissue is also believed to contain factors that aid tumor survival and growth. In pancreatic cancer, its density is thought to be a factor in preventing cancer-killing drugs from reaching the tumor.

David Tuveson's team used pancreatic organoid technology to learn something important about the problem of stroma in pancreas cancer. For the first time, their pancreatic organoids were "co-cultured" with one component of the stroma in which human tumors grow. The result was a more realistic rendering of what happens in patients.

The additional factor was CAFs (cancer-associated fibroblasts), which act like factories in the tumor, producing connective tissue. The team discovered that there are at least two varieties of CAFs in pancreatic cancer. Each seems to be involved in different ways. One fibroblast subtype produced a protein called αSMA; it contributes to the formation of dense stroma. The other, which secretes immune factor IL-6, has been separately linked to cancer cell proliferation.

Discovery of the heterogeneity of the fibroblast population in pancreas cancer opens up the possibility of selectively targeting these populations to make treatments more effective.

### *An Epigenetic Explanation of Metastasis*

C. Vakoc

Although cancer is well understood to have genetic causes, the factors responsible for its ability to spread have eluded scientists. Results obtained by a team led by Chris Vakoc, which included researchers in David Tuveson's lab, make a case for metastasis to have epigenetic roots—that is, critical changes in the chemical modifications on the chromosomes that do not change the underlying DNA sequence. The team used organoid technology to compare normal pancreatic ductal cells in mice with cells from the same animals in three distinct stages: premalignant, malignant, and metastatic.

Compared with cells in noncancerous and tumor-derived organoids, those in metastatic ones displayed an extraordinary number of alterations in regions called enhancers. These genome elements are present in all cells and are used by cells to turn on genes. "We show that to metastasize, the cell has to change, in effect, its whole telecommunications network—its enhancers are being reprogrammed," Vakoc says.

The team tracked down the molecular agent whose increased activity causes the reprogramming. Called FOXA1, it is typically active early in a cell's life, but dormant later on. In cancer, FOXA1 activity enables a cell to return to a developmentally primitive state—one in which the pancreas is being formed, and cells are multiplying and moving around, assuming the positions that characterize the maturing organ.

The new evidence of cancer cells acquiring the ability to spread by "remembering" a developmental program dormant since their earliest days "means that every cell, in a sense, is like a loaded gun," Vakoc says.

### *Improved Genome Reveals Maize's Remarkable Adaptive Potential*

D. Ware

A new, much more detailed reference genome for maize, or corn, was published this year by a team led by Doreen Ware and her colleagues at CSHL and around the globe. In its accounting of the sequence of nucleotides in the plant's 10 chromosomes, the new version, which was obtained for a small fraction of the cost of the first reference genome for the plant, published in 2009, helps us understand as never before why maize is the most productive and widely grown crop in the world.

Among many other things, the new sequence reveals that maize individuals are much less alike genomically than people are. This reflects its remarkable flexibility. This flexibility not only helps explain why maize has been so successful since its adaptation by agriculturalists thousands of years ago, but also bodes well for its ability to grow in new places as the earth's climate changes and for increasing the plant's productivity and environmental sustainability in the United States and abroad.

The new research demonstrates that in trying to determine what possibilities are available to a plant when adapting to new or changing conditions, it is just as much the context in which genes are activated—or silenced—as the identity of the genes themselves that determines what the total set of genes enables a plant to do.

## Public and Private Support

The year 2017 vividly demonstrated how CSHL is changing the landscape of biology. New York State Governor Andrew Cuomo and other state and local officials joined CSHL trustees and leadership to break ground on the renovation of the Demerec Laboratory, the focal point for a new CSHL research initiative to establish linkages between the development of cancer and nutrition, obesity, and metabolism. The $75 million effort is possible thanks to funds raised by the 125th Anniversary Capital Campaign and a grant from New York State.

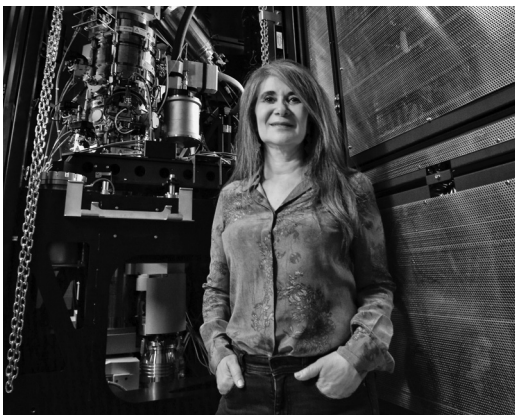
Breaking ground on the renovation of the Demerec laboratory.
Bruce Stillman is *third from left* and Governor Andrew Cuomo is in the *center*

CSHL's historic commitment to widespread and effective dissemination of scientific knowledge was enhanced by the growing momentum of bioRxiv, a bold Laboratory initiative creating the first preprint server for the life sciences.

In its fourth year of operation, bioRxiv is transforming how life scientists communicate. Preprints are complete but unpublished manuscripts of research papers, distributed online by their authors for discussion by the scientific community before consideration by peer-reviewed journals. Submissions have soared, more than doubling in 2017 to a total of some 17,000 manuscripts from researchers in more than 100 countries.

In recognition of bioRxiv's role in accelerating science, generous support was received in May from the Chan Zuckerberg Initiative, which will make possible continued expansion and a variety of technology upgrades and innovations.

With support from Mercer Family Foundation, the Laboratory now has a state-of-the-art Cryo-EM Facility designed for optimal operation of an FEI/Thermo Fisher Titan Krios G3. Led by Professors Leemor Joshua-Tor and Hiro Furukawa, and managed by Dennis Thomas, this facility is for biologists who seek to define the detailed structure of molecules and allows researchers to obtain near-atomic-level 3D images. The CSHL Shared Resource for Animal Imaging &



Leemor Joshua-Tor with the Thermo Fisher Titan Krios G3

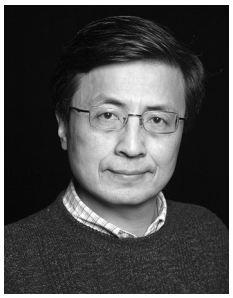
H. Furukawa

Tissue Imaging, which provides access to the most advanced noninvasive imaging modalities, tissue imaging, and pathology, was opened in 2017. The new facility is critical to the work of CSHL's National Cancer Institute–designated Cancer Center in testing potential cancer therapeutics and was funded by David H. Koch, in addition to an anonymous donor, and funds from New York State. Researchers can now visualize a broad range of tumor-associated parameters without invasive procedures, obtain high-quality tissue sections, and access extensive pathology services.

With $50 million over 5 years committed in grant funding from the National Institute of Mental Health (NIMH), CSHL is proud to be part of the BRAIN Initiative Cell Census Network (BICCN). Under this initiative, led by Professor Josh Huang, CSHL this year established a Center and a "Collaboratory" for the Mouse Brain Cell Atlas. Many of CSHL's neuroscience faculty have secured BRAIN Initiative grants, including Jesse Gillis, Pavel Osten, Partha Mitra, and Tony Zador. Additional Brain Initiative funding was secured to support Pavel Osten, Tony Zador, Adam Kepecs, and Bo Li.

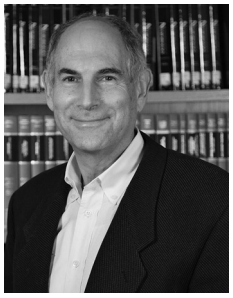
The Wellcome Trust and the Simons Foundation are supporting the International Brain Lab, an initiative including CSHL investigators that seeks to develop theories of how the brain works by focusing on a single behavior shared by all animals: foraging. Among the executive leaders of the global program are Associate Professor Anne Churchland and Professor Tony Zador.

CSHL's Annual Fund raised a record $7 million in unrestricted funds through many successful events, including the Double Helix Medals Dinner honoring Tom Brokaw and Helen and Charles Dolan; the Women's Partnership for Science, celebrating CSHL Association honorary director Freddie Staller; and the Golf Tournament, applauding Mark Hamer.



J. Huang

J. Berger-Sweeney



S. Weisbrod

T. Brokaw

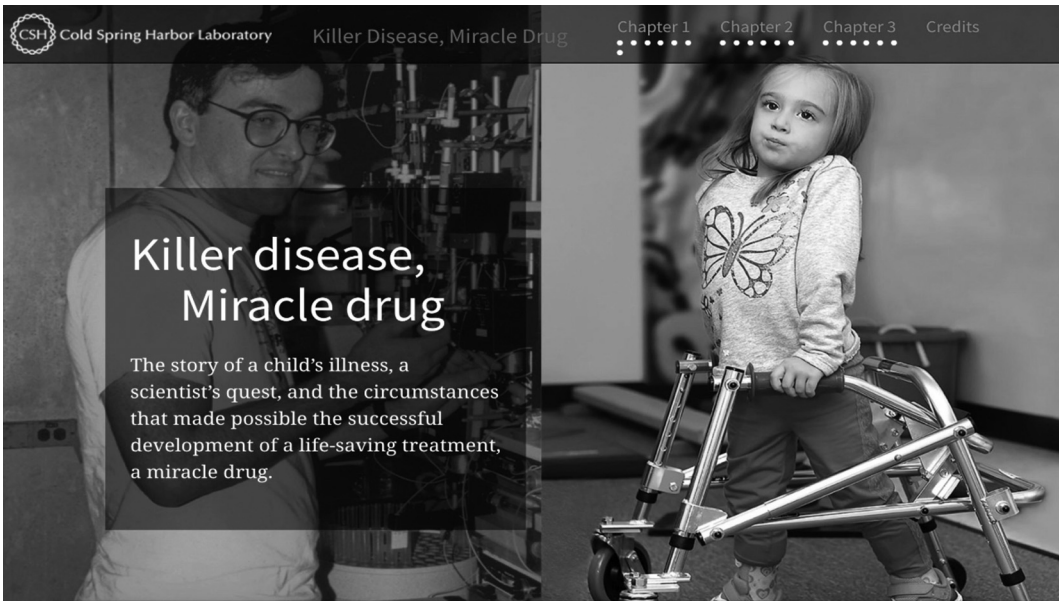
## Board of Trustees

The Board of Trustees welcomed two new members: Joanne Berger-Sweeney, Ph.D., President of Trinity College, and Stuart Weisbrod, Ph.D., Chief Investment Officer of Iguana Healthcare Partners, a healthcare investment fund focusing on public equities.

Berger-Sweeney became President of Trinity College in 2014 after serving as Tufts University Dean of the School of Arts and Sciences. Prior to this, she was an associate dean and faculty member at Wellesley College. Berger-Sweeney received an undergraduate degree in psychobiology from Wellesley College and an M.P.H. in environmental health sciences from the University of California, Berkeley. She has a Ph.D. in neurotoxicology from the Johns Hopkins School of Public Health, where she did the proof-of-concept work on Razadyne, the second-most-used Alzheimer's drug in the world.

Helen and Charles Dolan

L. Joshua-Tor




Weisbrod first came to CSHL as a postdoctoral fellow after receiving a Ph.D. in biochemistry from Princeton University. He then pursued an MBA at Columbia University and began a biotech investment career capped by the founding of Merlin Biomed and later Iguana Healthcare Partners.

## Research Faculty Awards

Professor and Howard Hughes Medical Institute Investigator Leemor Joshua-Tor was elected to the National Academy of Sciences as one of 84 new members and 21 foreign associates recognized for "their distinguished and continuing achievements in original research." She also joined the ranks of the American Academy of Arts and Sciences.

M. Egeblad

Joshua-Tor's laboratory studies the molecular basis of nucleic acid regulatory processes—RNA interference (RNAi), and DNA replication in particular. They use the tools of structural biology, biochemistry, and biophysics to study proteins and protein complexes associated with these processes to elucidate how they work.

The first ever drug to treat a lethal childhood disease called spinal muscular atrophy, Spinraza®, won the 2017 Galien Prize for Biotechnology Breakthrough of the Year. Marketed by Biogen, the drug was developed by Ionis Pharmaceuticals Inc. with technology licensed from and in collaboration with Professor Adrian Krainer's laboratory. Adrian was also named Inventor of the Year by the New York Intellectual Property Law Association.

Associate Professor Mikala Egeblad won the Pershing Square Sohn Cancer Prize, which will support her work to understand the relationship between chronic inflammation and the metastatic recurrence of breast cancer. Her team will explore the role of neutrophils, a specific type of immune cell involved in the awakening of dormant cancer cells. Neutrophils can form neutrophil extracellular traps (NETs) as part of the body's reaction to inflammation. By targeting NETs, Egeblad and her team hope to be able to prevent cancer recurrence in certain cases.

D. Spector

David L. Spector, Ph.D., the Laboratory's Director of Research, was named a fellow of the American Society for Cell Biology (ASCB). A member of the CSHL faculty since 1985, Spector is a pioneer in advancing our understanding of the inner workings of the cell nucleus, researching the organization and regulation of gene expression in living cells. He is the first CSHL faculty member to receive this honor.

In recognition of her efforts to promote and mentor women in neuroscience, Associate Professor Anne Churchland was honored with the Louise Hanson Marshall Special Recognition Award at the Society for Neuroscience's 2017 Annual Meeting in November. Each year, the award goes to "an individual who has significantly promoted the professional development of women in neuroscience through teaching, organizational leadership, public advocacy, or other efforts that are not necessarily research-related."

A. Churchland

Churchland has garnered attention from the neuroscience community and beyond for her pioneering website, Anne's List, aimed at alleviating bias against women in science—specifically, as reflected in the paucity of invited female speakers at scientific conferences. Anne's List gathers female scientists' names, research topics, and seniority levels in order to help conference organizers easily identify women whom they might invite to speak on a particular subject. Churchland is also a faculty advisor for the group Women in Science & Engineering (WiSE) at CSHL. Her work on Anne's List helped inspire CSHL WiSE to team up with CSHL's Meetings & Courses division to create a larger Women in Biology Speakers List.

T. Engel

## Promotions and New Hires

The Laboratory welcomed Assistant Professor Tatiana Engel to CSHL's Swartz Center for Computational Neuroscience, where she is focused on the dynamics of neural circuits.

Monn Monn Myat, Ph.D., is the new Associate Dean of the Watson School of Biological Sciences.

M.M. Myat

## CSHL-Northwell Affiliation 2016–2017 Progress

During the second year of the strategic partnership between CSHL and Northwell Health System, we established an infrastructure that allows clinicians and basic scientists to easily share patient samples. Through these efforts, CSHL received tissue samples from 140 Northwell Health patients. These samples bring clinical data into the laboratory, and they are being used to identify genes that drive cancer and to test potential new therapies. The affiliation is also expanding translational research to make a direct impact on patient care. This means bringing discoveries out of the laboratory and into the clinic.

We want to ensure that the next generation of doctors has the tools and knowledge they need to bridge the gap between basic science and patient care. This includes expanding upon and developing new education initiatives that promise to transform the way young doctors are trained in clinical research. Medical students from the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell continue to participate in research during their summers, and next year we hope to bring on a Translational Research Fellow through the National Resident Matching Program.

The original 2015 agreement was amended to include a small component for neuroscience. Now, the affiliation will fund high-impact projects to increase translational research in both neuroscience and cancer. Over the past year, the Joint Steering Committee has funded eight new collaborative research proposals for a total of 28 ongoing projects.

The affiliation has sponsored international cancer conferences and meetings held at CSHL, including Automatic Pathology and Making Oxidative Chemotherapy Less Toxic. CSHL was awarded a subcontract by Leidos Biomedical Research to lead a Cancer Model Development Center for multiple cancers. Drs. David Tuveson and David Spector will lead the international effort with Dr. Hans Clevers of the Hubrecht Institute, Drs. Aldo Scarpa and Vincenzo Corbo of the ARC-Net Centre for Applied Research on Cancer at the University of Verona, Italy, and Dr. James

R. Barakat

Crawford of Northwell Health and Dr. Peter Gregersen of Northwell Health's Feinstein Institute for Medical Research.

Northwell Health has continued efforts to build out a Phase 1 Experimental Therapeutics Unit to be led by Dr. Robert Maki, who holds a joint appointment at CSHL and Northwell.

The affiliation announced the hiring of Dr. Richard Barakat, Physician-in-Chief and Director of the Northwell Health Cancer Institute, Senior Vice President of the Cancer Service Line and Professor of Obstetrics and Gynecology at the Zucker School of Medicine at Hofstra/Northwell.

## Business Development & Technology Transfer

Engaging industry and investor partners is a means to bring CSHL's innovation to the world while providing the business with resources, capital, and philanthropic funding, as well as a competitive advantage in the commercialization of an innovation if it is intellectual property. We look to these industry partners not only for investments, but also for consultative business development guidance in an ever-more-complicated business climate. A goal is to find excellent sponsored research partners, and the number and value of these engagements has increased significantly in the past 3 years. We have moved from sourcing, negotiating, and signing one or two arrangements a year to completing eight to 10 per year, involving a variety of industry partners and CSHL labs.

This year we evolved our approach to engaging industry and investors. In cooperation with the Development Department and the Meetings & Courses Program, we have introduced potential industry partners and investors to the Banbury Center, Meetings & Courses Program sponsorship opportunities, donor engagement, and postdoc and graduate student career discussions, as well as research collaborations.

Dr. R.K. Narayan, Ph.D., joined the team as Director, Technology Transfer, with an initial emphasis on operations and compliance matters, and as a lead for technology transfer matters in neuroscience. We also added to the Executives in Residence and Entrepreneurs cadre of business executives, who advise faculty on commercial aspects of their work and serve on the Boards of some of CSHL's spin-out companies: Kate Delgado, CSHL Entrepreneur in Residence, and Peter Young, CSHL Executive in Residence.

In 2017, while focusing on the management of existing agreements and assets, compliance and risk mitigation, we concluded the following:

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|---|---|
| License/option agreements: | 3 |
| Sponsored research agreements: | 9 |
| Material transfer agreements: | 142 |
| New patent filings: | 12 |

## Education Programs

### *Meetings & Courses Program*

CSHL Meetings this year attracted 7,300 participants to the main campus. The 82nd Cold Spring Harbor Symposium, Chromosome Segregation & Structure, addressed the enormous progress in this field, attracting almost 300 participants, including many of the world's leading chromosome biologists. The year saw the continuation of many successful annual and biennial meetings, as well as the introduction of several new meetings. The meetings program is supported by grants from the National Institutes of Health, the National Science Foundation, and the newly invigorated Corporate Sponsor Program.

The Cold Spring Harbor Asia (CSHA) conference program held 17 scientific conferences in Suzhou, China, attracting more than 3,250 scientists. CSHA's scientific program, which includes symposia and meetings and occasional Banbury-style discussion meetings, is designed for scientists from the Asia/Pacific region, who make up more than 80% of attendance. The program is supported with a major sustaining grant from the Suzhou Industrial Park, where the program is headquartered.

The Courses program has played an important role in the history of molecular biology and life science, propagating important new techniques, methods, and ideas among scientists at all career stages. Covering a diverse array of topics in molecular biology, neurobiology, structural studies, and bioinformatics, 750 instructors, lecturers, and assistants have come to teach at CSHL from universities, medical schools, research institutes, and companies around the world. In 2017, 600 trainees—advanced graduate students, postdocs, and faculty—attended courses lasting from 1 to 3 weeks.

The Courses program relies on grants and foundation support, including major support from the Helmsley Charitable Trust, Howard Hughes Medical Institute, National Institutes of Health, and National Science Foundation. The Helmsley Interdisciplinary Fellowship Fund provided major funding to 125 scientists to participate in CSHL courses outside their primary disciplines. The Courses also benefit from the loan of equipment, reagents, and technical support from many companies, whose support is indispensable to ensure that the program remains cutting-edge.

### *Watson School of Biological Sciences*

In 2017, the Watson School welcomed its 19th incoming class and graduated its 14th. 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-six graduates have now secured tenure-track faculty positions and are receiving federal grants and publishing papers as independent researchers. Eight of them have already been promoted to associate professor, and Zachary Lippman became the first to be promoted to full professor, here at CSHL. The School's graduates have also moved into influential positions in administration, publishing, consulting, and industry.

At the 2017 graduation ceremony, eight WSBS students were awarded Ph.D. degrees, bringing the total since the School's inception to 98.

2009 Nobel laureate Carol Greider received an honorary Doctor of Science degree at WSBS graduation. She earned her Ph.D. at the University of California, Berkeley, where as a graduate student in 1984, working with Dr. Elizabeth Blackburn, she discovered telomerase, an enzyme that maintains telomeres—the "caps" at the end of chromosomes. In 1988 Dr. Greider came to Cold Spring Harbor Laboratory, where, as the Lab's second CSHL Fellow, she cloned and characterized the RNA component of telomerase. In 1990 she was appointed an Assistant Investigator and in 1994 an Investigator. In 1997 Dr. Greider moved her laboratory to the Johns Hopkins University School of Medicine. Today she is Daniel Nathans Professor and Director of Molecular Biology and Genetics at the university.

During the year, scientific papers published by students of the School appeared in major journals, bringing the cumulative total to more than 365. Current and former students won prestigious and highly competitive scholarships and fellowships, as in past years. In August, the WSBS welcomed eight new students. Members of the Class of 2017 were selected from more than 200 applicants. Other new graduate students entered as visitors from other institutions, including 10 from Stony Brook University.

2017 WSBS graduation

From June through August, 20 undergraduates from around the United States, as well as China, Greece, and Pakistan, had the remarkable opportunity to perform advanced research in the laboratory of a CSHL faculty member. This immersive experience brought intellectual as well as social rewards for the participants, as in past years. The URP (Undergraduate Research 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.

### *Banbury Center*

The year 2017 was one of transition for the Banbury Center, the Laboratory's science policy think tank. Dr. Jan Witkowski, the founding director, handed the baton to Dr. Rebecca Leshan after 30 remarkable years of cultivating critical scientific discourse at the Center. In his speech, "How Scientists Work," at Banbury's 1977 dedication ceremony, Francis Crick pointed to small meetings as the best way for scientists to share and inspire new ideas and strategies. Activities at Banbury continue to be guided by this concept; its mission is to further scientific knowledge and the well-being of society.

Banbury meetings in 2017 spanned discovery and translational science, public health, policy, education, and innovation, reflecting the ever-growing need for multisector and multidisciplinary engagement at small meetings across a broad range of issues. A total of 536 individuals took part in these Banbury meetings, with 72% marking their first occasion. Participants were drawn from 28 countries on six continents.

In 2017 Banbury continued to attract financial support from across sectors, with more than half drawn from not-for-profit organizations. Five of 2017's meetings built on a strong history in neuroscience and cancer. Public health was the subject of several productive meetings, including Maximizing Impact of New HIV Prevention Technologies in Sub-Saharan Africa and Protective Immunity & Vaccines for Lyme Disease. A report on next-generation Lyme disease diagnostics was published in *Clinical Infectious Disease*, based on a 2016 Lyme disease meeting at Banbury.

NLR17 group meeting at Banbury

### *DNA Learning Center*

The DNA Learning Center continues to spread its hands-on approach to teaching biology and genome science to students across the globe. A licensed DNA Learning Center established in China in 2014 at Beijing No. 166 Schools now extends to include middle school as well as high school students. In 2017, a teacher-training program and a DNA barcoding citizen science project for high school students were also started there.

Barcode Beijing, modeled on student DNA barcoding projects that have succeeded on Long Island and in New York City schools, involves middle/high school students in independent, student-driven research projects that use DNA sequencing to study biodiversity in their own environs. Using a single, standardized chemistry and bioinformatics platform, students explore many aspects of the urban environment—wildlife in homes and parks, species used in commercial products, insect disease vectors, introduced species, and food mislabeling.

Another novel concept that the DNALC has helped to successfully propagate internationally is the Breakthrough Junior Challenge. Begun in 2015, it is a global competition in which precollege students produce short videos explaining an important concept in life sciences, mathematics, or physics. Funded by Mark Zuckerberg and Priscilla Chan and Yuri and Julia Milner, the Junior Challenge is a complement to the prestigious Breakthrough Prize, designed to inspire creative thinking about fundamental concepts in the life sciences, physics, or mathematics. In addition to a $250,000 scholarship, winners receive a DNALC-designed and -equipped $100,000 science lab for their schools.

This year, in fulfillment of an award in the competition won last year by Hillary Diane Andales from the Philippines, the DNALC established a training lab at the Eastern Visayas Campus of the Philippine Science High School and trained local teachers so that all 14 campuses of the Philippine national science high school system can benefit from the new school lab classroom.

In the New York metro area this year, 21,000 students attended labs at Dolan DNA Learning Center, DNALC West, and Harlem DNA Lab. An additional 9,000 students completed labs in school led by DNALC staff, and 1,400 students attended week-long camps. Also this year, 6.4 million visitors accessed DNALC's suite of multimedia resources online, including 4.6 million visits to DNALC websites, nearly one million views of YouTube videos, and more than 815,000 downloads of smartphone/tablet apps, the 3D Brain, Weed to Wonder, and Gene Screen.

Breakthrough lab at the Philippines High School

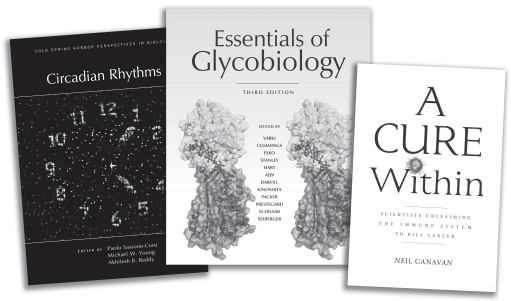
### *Cold Spring Harbor Laboratory Press*

Science is a global enterprise that depends on the timely communication of ideas and results. The Cold Spring Harbor Laboratory Press provides scientists worldwide with authoritative, affordable, and pertinent information to further their research and aid in their career development. The CSHL Press has taken a creative approach to challenges that have attended the rise of digital media.

Its three newest peer-reviewed subscription journals—*Cold Spring Harbor Protocols*, *Cold Spring Harbor Perspectives in Biology*, and *Cold Spring Harbor Perspectives in Medicine*—enjoy considerable success. Each transforms content that in former years might have appeared only in print book form, rendering it in a digital, readily discoverable, and reusable serial form.

The newest journal, *Cold Spring Harbor Molecular Case Studies*, reimagines the traditional case report in medicine to enable open sharing of insights that genomic and molecular analysis bring to the causes and potential treatment of disease.

*Genes & Development* and *Genome Research* remain at the top of their disciplines among primary research journals. Both titles are in the top 1% of the 8,000 journals ranked in the Science Citation Index.




Some 2017 books

The CSHL Press published 18 new book titles in 2017, adding to its list of more than 200. Highlights including topical volumes on malaria biology (supported by the Flowers Foundation), tissue engineering and regenerative medicine, prion diseases, and the biology of exercise. *A Cure Within: Scientists Unleashing the Immune System to Kill Cancer*, by Neil Canavan, tells the story of immune-oncology pioneers whose work has resulted in two FDA-approved T-cell-based therapies for cancer.

### *Library & Archives*

The 2017 Sydney Brenner Scholar is University of Manchester Professor Matthew Cobb, who is researching the two-decade collaboration between Francis Crick and Sydney Brenner.

Previous Sydney Brenner Scholar Miriam Rich, who is a History of Science graduate student at Harvard University, presented a seminar titled Defects of Development: Embryology & Eugenic

Concepts of Race. This talk was part of the "Conversations on the History of Eugenics," which also included talks and a panel discussion with Library and Archives Executive Director Mila Pollock, historian Elof Carlson, and the Executive Director of the DNA Learning Center, David Micklos.

The CSHL Archives increased this year with several donations. Nobel laureate Carol Greider donated 30 linear feet of laboratory notebooks and laboratory films, which includes the notebooks detailing her Nobel-winning graduate work on telomeres with Elizabeth Blackburn. A donation of an additional 6 linear feet of materials spanning 1950–2008 for the Barbara McClintock Collection came from McClintock's niece, Marjorie Bhavnani. Dr. Winship Herr, former Assistant Director of the Laboratory and Founding Dean of the Watson School of Biological Sciences, donated an additional 6 linear feet of materials to the Winship Herr collection. These personal communications and administrative materials illuminate the effort to gain Ph.D.-granting accreditation from the Board of Regents of the University of the State of New York.

The Archives created an online digital exhibition for the Amar Klar Memorial from archival materials and photographs.

The Library and Archives and Genentech Center for the History of Molecular Biology and Biotechnology, in collaboration with the Laboratory's Meetings & Courses Program, continued its History of Science annual meeting series with 40 Years of mRNA Splicing: From Discovery to Therapy. The meeting, co-organized by Mila Pollock, Phil Sharp, and Joan Steitz, brought together more than 270 of the most important mRNA splicing researchers, including six Nobel laureates. The meeting also brought back our alumni Rich Roberts, Louise Chow, and Richard Gelinas, who told the story of the discovery of mRNA splicing.

Other Library events included a talk on premodern neurosurgery by Dr. Eugene Flamm of Montefiore Medical Center, a celebration of women in STEM fields as explored through books in our Library written by and about women, and a series of seminars, cohosted with the Post Doc Liaison Committee on Perspectives on Science Careers.

40 Years of mRNA Splicing: From Discovery to Therapy meeting

For the second year, the Library offered a multischool journal club, bringing 15 high school students from Long Island to the Laboratory to learn how to search for, identify, examine, and present scientific publications.

## Infrastructure

Reconstruction of the Demerec Laboratory began in earnest in 2017. This major project comprised a complete redesign and reconstruction of a ca. 1953 laboratory building. This historic building has been home to some of CSHL's most honored researchers, including Nobelists Barbara McClintock, Alfred Hershey, Rich Roberts, and Carol Greider. New York State contributed $25 million to fund this renovation that involved extensive demolition of the original structure and relocation of many researchers to renovated lab spaces in the Beckman, Jones, and McClintock laboratories. Completion of this project is expected in April 2019.

Modernization of Dolan Hall, a ca. 1991 dormitory, will allow for 60 private rooms with en suite bathrooms. The project was divided into two halves to allow for continued use of the property by Meetings & Courses Program participants while renovations took place. Completion is anticipated in early 2019.

The Olney barn was a ca. 1880 barn originally built alongside the Olney House. Its condition had deteriorated to render the structure unsalvageable. A cosmetically similar replacement structure was built during 2017 to accommodate the need to store and maintain grounds equipment.

The Cryo-EM Facility was constructed this year to house a new, state-of-the-art electron microscope. It is a dedicated isolated facility that has been retrofitted into an existing building, the Beckman Laboratory. This project required complete isolation of the facility from the rest of the building, including isolated ventilation, isolated power, and active electromagnetic shielding.

## Community Outreach

CSHL was pleased to work with local area organizations on events that furthered our mutual interests, including the Children's Heart Foundation, Energeia, Friends of TJ, Leukemia and Lymphoma Society, Suffolk County Estate Planning Council, the Lustgarten Foundation, LIA Young Professionals Committee, ALS Association of Greater NY, the Huntington Hospital Board, and the Animal Cancer Foundation.

Cryo-EM facility

Open House

### *2017 Open House*

CSHL welcomed 500+ new friends to campus on June 10 to share the thrill of scientific discovery. Led by the Public Affairs Department, more than 80 CSHL volunteers representing the institution's scientific research and education expertise in genetics and molecular biology helped explain to guests how work at CSHL benefits society.

Guests engaged in hands-on experiments, toured laboratories, and interacted one-on-one with CSHL scientists, learning more about DNA, plant biology, cancer research, neuroscience, and quantitative biology. A special program of half-hour science talks covered topics as diverse as mapping the brain with barcodes, demystifying GMOs, meeting Ötzi the iceman, and how scientists are attacking metastatic breast cancer with new tools found in the genome's "dark matter."

In addition to the campus tours provided at the Open House, the tour guide team of 17 graduate students gave 67 group tours to more than 1300 guests and 16 public tours for more than 250 participants.

First graders from neighboring Cold Spring Harbor School District's Goosehill Primary School and Friends Academy participated in a hands-on science fair consisting of six stations. At each station, the students learned about various scientific principles (from the brain and magnetism to DNA codes and enzymes) through activities and instruction conceived, planned, and led by Watson School graduate students and DNALC teachers. The participants included 120 students accompanied by 10 teachers and more than 100 parents during the 2 days.

Expanding CSHL's capabilities to engage audiences, on-demand and on mobile devices, around the world, the Public Affairs Department launched a technology upgrade to cshl.edu. Together with increased efforts to develop new digital content and leverage social media channels, the Laboratory research and education developments are being communicated as multimedia stories that can be more readily understood by individuals not formally trained in science. The cshl.edu website is the platform for the Lab's external communications programs.

### *CSHL Public Lectures*

**March 1: Rob Martienssen, Ph.D.**, Professor, Cold Spring Harbor Laboratory: *Cocktails & Chromosomes*.

**May 24: Adam Kepecs, Ph.D.**, Professor, Cold Spring Harbor Laboratory: *Cocktails & Chromosomes*.

**June 14: Adam Siepel, Ph.D.**, Professor, Cold Spring Harbor Laboratory; Chair, Simons Center for Quantitative Biology: *Reconstructing Ancient Human History from DNA*.

**July 25: Douglas Fearon, M.D.,** Professor, Cold Spring Harbor Laboratory; **Robert Maki, M.D., Ph.D.**, Professor, Hofstra Northwell School of Medicine and Professor, CSHL: *Immunotherapy & Cancer—The Latest Research*; cosponsored by CSHL, US Trust, Northwell Health, and St. Johnland Nursing Center.

**August 23: Michael Ronemus, Ph.D.**, Research Assistant Professor, Cold Spring Harbor Laboratory: *Cocktails & Chromosomes*.

**October 19: David Jackson, Ph.D.**, Professor, CSHL; **Zachary Lippman, Ph.D.**, Professor, CSHL; **Doreen Ware, Ph.D.**, Adjunct Associate Professor, CSHL & USDA Agricultural Research Service: *The Changing Relationship between Humans and Plants—"It's Complicated."*

**October 25: Gurinder "Mickey" Atwal, Ph.D.**, Associate Professor, Cold Spring Harbor Laboratory: *Cocktails & Chromosomes*.

**November 5: Jonathan Weiner**, Pulitzer prize–winning author and Maxwell M. Geffen, Professor of Medical and Scientific Journalism, Columbia Journalism School: *LONG FOR THIS WORLD—Writing about Immortality … and Other Controversial Topics in the Science of Life*; 2017 Lorraine Grace lectureship on societal issues of biomedical research.

### *CSHL Public Concerts*

**April 21**: Gleb Ivanov and Dmitri Berlinsky, piano and violin
**April 28**: Anna Polonsky and Orion Weiss, piano duo
**May 5**: Jocelyn Ho, piano
**August 25**: Verona Quartet, string quartet
**September 8**: Matthew Graybil, piano
**September 15**: Tchaikovsky Trio

Verona Quartet

## Looking Forward

CSHL breakthroughs in research and education will undoubtedly change the world for the better, and I thank all of those who contributed to the Laboratory's mission in 2017.

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