Highlights of the Year

Research

Hundreds of scientists working in Cold Spring Harbor Laboratory's 50-plus laboratory groups contributed to research that in 2019 was published in the world's major research journals. Their efforts reflect the full spectrum of this institution's scientific activity in cancer, neuroscience, plant biology, quantitative biology, and genomics. The following is a sampling of this year's important findings.

Machine Learning Better Interprets Gene Regulation

J. Kinney

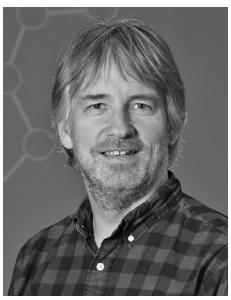
Machine learning algorithms are helping biologists make sense of molecular signals that control how genes function, but algorithms developed to analyze larger and larger sets of data become increasingly complex and difficult to interpret. Associate Professor Justin B. Kinney has an approach to design advanced machine learning algorithms that are easier for biologists to understand.

The algorithms are a type of artificial neural network (ANN). Inspired by the way neurons connect and branch in the brain, ANNs are the computational foundations for advanced machine learning. Biologists use ANNs to analyze data from an experimental method called a "massively parallel reporter assay" (MPRA), which investigates DNA. Using this data, quantitative biologists can make ANNs that predict which molecules control specific genes in a process called gene regulation.

Unfortunately, the way standard ANNs are shaped from MPRA data is very different from how scientists ask questions in the life sciences. Kinney's approach bridges this gap between computational tools and how biologists think. These custom ANNs mathematically reflect common concepts in biology concerning genes and the molecules that control them, forcing data to be processed in a way that a biologist can understand. Kinney's laboratory is now investigating a wide variety of biological systems, including key gene circuits involved in human disease.

One Gene Balances Plant Growth versus Immunity

With an unpredictable array of bacteria, fungi, and viruses in the soil and air, a plant needs a robust immune system. But energy spent on pathogen defense cannot be used to grow taller or produce seeds. In the wild, the trade-off is crucial. In a tended field, however, crop plants face fewer threats. One way to boost the productivity of a plant is to redirect some of its resources away from maintaining an overprepared immune system and into enhanced seed production.

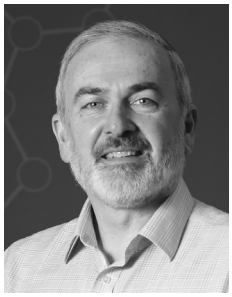


D. Jackson

As reported in the *Proceedings of the National Academy of Sciences*, Professor David Jackson and his team identified a gene in corn that contributes to both the plant's development and to the control of its immune system. Manipulating this gene could be a way to increase crop yields by reprogramming how a plant balances its investments in growth and defense. Most corn plants cannot survive without the gene, which is called *Gβ* (pronounced GEE beta) and encodes part of an essential signaling complex. Observing that seedlings lacking *Gβ* quickly turn brown and die, the researchers determined the gene helped to keep the plant's immune system in check.

By experimenting with dozens of genetically diverse lines of corn, the team found that some plants could grow without *Gβ*. Studying these plants, they discovered that *Gβ* impacts the size of a plant's meristems—reservoirs of stem cells from which new growth originates. The team also linked naturally occurring variations in the *Gβ* gene to the production of corn ears with unusually abundant kernels. *Gβ* is involved in both growth and immunity, and it likely mediates cross-talk between the cellular pathways that control these competing functions.

Mutant Cells Team to Make a Cancer Deadlier



A. Krainer

Professor Adrian Krainer and colleagues discovered that two cell mutations, already harmful alone, enhance one another's effects, contributing to the development of the deadly blood cancer acute myeloid leukemia (AML). In *Nature*, they detailed how mutations of the genes *IDH2* and *SRSF2* partner to cause AML.

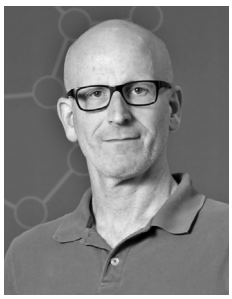
The presence of the *IDH2* mutation enhances the errors caused by the *SRSF2* mutation, preventing cells in the bone marrow from maturing into the red and white blood cells an AML patient needs to overcome the disease. Prior to this research, the only known similarity between the two mutations was that they are involved in precancerous symptoms. But in many cases, the cause of the symptoms is not the cause of cancer itself. "Just because you see a mutation [in a sick patient's cells] doesn't really show that it's directly contributing to the disease," Krainer said.

The researchers knew that one of the two mutations in question, in the *SRSF2* gene, causes errors in a crucial process called RNA splicing. Splicing converts messages from DNA, in the form of RNA, into readable instructions for a cell. Errors in this process can result in cell malfunction.

Previous research showed that these mutations were present in only 1% of AML patients. But the Krainer laboratory found that this problem is much more common, appearing ~11% of the time in AML patients.

The researchers discovered this by dusting for *SRSF2*'s fingerprints within the gene's actual workplace (RNA), instead of simply searching an entire office block (DNA). Further experiments revealed that the severity of the identified *SRSF2* splicing errors can be enhanced by the presence of a second mutation, in *IDH2*, resulting in even more defective blood cells. This interdependence suggests points of therapeutic intervention.

BARseq Builds a Better Brain Map



A. Zador

Professor Anthony Zador set out a decade ago to map three pillars of brain function: connectivity, gene expression, and physiological activity. His team developed MAPseq, a technique to map the connections of different brain cells and gain a better understanding of how they interact with each other. Improving the technique, Zador's team published BARseq, the next generation of MAPseq, in *Cell*.

The new technology can accurately pinpoint the location of a neuron. BARseq determines not only a neuron's connections, but also its pattern of gene expression and its physiological activity. "We wanted to understand how neurons are connected to one another and relate them to other aspects of neural function, like gene expression and neuronal activity," explained Zador.

The researchers used MAPseq to tag each neuron with a unique barcode composed of genetic sequences. By following those tags across the brain, they can see where the neurons send messages and then map the pathways those signals form between different areas of the brain. But the MAPseq tagging process made it difficult to see how a neuron mediated a particular function such as gene expression. BARseq tags and sequences the neurons in situ, or in their original form and location in the brain, so you can see exactly where the neurons are when the barcodes are sequenced.

The team used BARseq to map the connections of 3,579 neurons in the auditory cortex of the mouse brain. Matching connectivity patterns to gene expression allows scientists to characterize different cell types and define their specific functions in the brain. It could be a valuable tool for studying how neural circuits are formed, providing a foundation for understanding thought, consciousness, decision-making, and how those go awry in neuropsychiatric disorders like autism, schizophrenia, depression, and OCD.

Detailed New Primate Brain Atlas

Research conducted in Japan with contributing neuroscientists from CSHL resulted in a 3D reconstruction of a marmoset brain, as well as an unprecedented level of detail about neuronal connectivity across the entire brain. The study introduces a new methodology, combining experimental and computational approaches, that helps account for significant variation between individual brains. It allows for synthesizing unique brain connectivity maps into a single reference brain. The resulting data set for the marmoset brain may offer insights into human neural connectivity.

Professor Partha Mitra collaboratively led the study reported in *eLife* as part of Brain/MINDS research conducted at the RIKEN Center for Brain Science in Japan. The brain architecture of marmosets more closely resembles that of humans than does the mouse brain. Although mice are currently the mainstay for modeling human disease, the emergence of marmoset models of human neurological disorders has made marmosets a target of new research.

P. Mitra

"Brain connectivity studies have been carried out in the marmoset before," Mitra explains. "But we did not have complete three-dimensional digital data sets, showing connectivity patterns across several entire brains at the light-microscope resolution." With this new data and approach as a basis, neuroscientists are closer to making sense of the complex neural connections in the primate—and human—brain.

Novel Approach to MDS Cancer Treatment

CSHL Fellow Lingbo Zhang and colleagues discovered a new drug target for myelodysplastic syndrome (MDS), a common blood cancer with very few treatment options. Published in *Science Translational Medicine*, Zhang's research restores blood cell production in mice genetically engineered to mirror the pathological features of human MDS patients who are resistant to existing treatments.

L. Zhang

MDS is sometimes referred to as "bone marrow failure disorder." Bone marrow is designed to produce enough blood for everyday survival. When blood cells are lost via bleeding or when they grow too old to do their job, replacement cells are made and begin to mature. MDS results from those replacements being too few, defective, or both.

Traditional treatments for MDS symptoms rely on the body's natural ability to make more mature red blood cells, which is driven by a hormone called erythropoietin (EPO). Immature red blood cells developing in the bone marrow must be exposed to EPO to fully mature into red blood cells that can aid the body. Delivering lots of EPO to the bone marrow does not help MDS patients because many do not have enough immature blood cells to begin with.

Zhang and his colleagues looked to an even younger stage of the developing blood cells as a point of intervention. They discovered that activating a specific protein receptor called CHRM4 significantly hampers the maturation of cells responsive to EPO. By blocking this receptor, Zhang and his colleagues were able to restore healthy blood cell production. In mice, this strategy significantly improved survival rates.

Mice Fidget When Deep in Thought

Almost everyone fidgets, even mice. In *Nature Neuroscience*, Associate Professor Anne Churchland and colleagues observed that the neural activity of mice performing trained tasks indicates that they fidget while making decisions.

A. Churchland

Churchland's laboratory investigates the neural circuits that are connected to decision-making. They studied the neural activity all across one part of the brain in a mouse while it was engaged in decision-making tasks. They measured the activity with wide-field

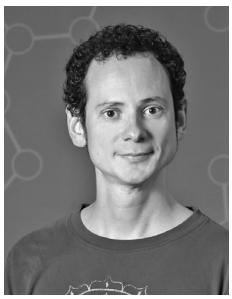
imaging, like an fMRI (used for mapping brain activity) for a mouse, allowing them to see the activity of neurons across a large portion of the brain all at the same time.

The mice were trained to grab little handles to initiate a trial and lick one way or the other to report their decisions. The scientists expected to see neural activity related to the handle grabbing or with licking. What they saw was that one simple task set off electrical activity across the mouse brain and found that most of that activity was driven by uninstructed movements that the animal was making such as hind-limb movements, pupil dilations, facial movements, nose movements, and whisker movements. "We originally thought the animals were 100% focused on our task—the licking, the grabbing, and the deciding—but it turned out that they had their own set of priorities that involved a lot of movements of all different kinds."

For scientists researching cognition, the results suggest greater attention to discerning signals uniquely related to cognitive processes and signals related to background movements. Researchers will have to work to disentangle the two signals, and this study provides guidelines and computational codes on how to correct for it.

Churchland speculates that movements are more tightly connected to cognition than previously recognized. "Maybe the movements are part of the process of thinking and deciding," she said.

Quantifying How the Brain Smells



F. Albeanu

A. Koulakov

To understand how the brain processes and interprets smells, Associate Professor Florin Albeanu and Professor Alexei Koulakov put past odor-classifying models to the test and discovered discrepancies.

Their results, in *Nature Neuroscience*, differ from other published studies that found predictable relations between molecular properties of odors and activity in the early stages of the olfactory system. The new research found that although there were some correlations between some molecular properties of odors and corresponding neuron activity response, they "held little predictive power when new odor pairs or shuffled properties were tested."

Generally, scientists know that odor particles first enter through the nasal cavity, where odorant receptors expressed by olfactory receptor neurons in the sensory tissue bind to them. The olfactory bulb, a structure located in the forebrain of mammals, then processes information from the receptors. Afterwards, the bulb sends out this information to several higher processing brain areas, including the cerebral cortex. There, the olfactory output messages are further analyzed and broadcast across the brain before they are conveyed back to the bulb in a feedback loop.

"Rich feedback makes the olfactory system somewhat different from the visual system," Koulakov said. "Olfactory experience is very subjective—perception of smells actually depends on the context, and on an individual's prior experience."

Albeanu and Koulakov suggest that the entry level of olfactory inputs and the further processed bulb outputs reflect different aspects of smell. The unexpected results of their research are an exciting opportunity to build a more comprehensive and testable computational model for the odor space that captures the differences in informational relevance for scent features across the various levels of olfactory processing.

Architecture of Norovirus Informs Vaccine Development

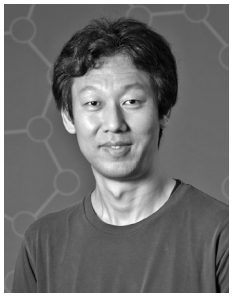
Noroviruses are a leading cause of food-borne illness outbreaks, accounting for 58% of all outbreaks and causing 685 million cases worldwide each year. There is no effective therapeutic against them. Knowledge of the intricate structure of the outer layer of noroviruses, the capsid, which allows the virus to attach to its human host, is key to vaccine development. In vaccines, specific antibodies recognize the capsids and bind to them so they can no longer interact with human cells.


L. Joshua-Tor

Professor Leemor Joshua-Tor led a team to solve the high-resolution structures of four different strains of noroviruses using a cryo-electron microscope. This allowed them to see the intricate architecture of virus shells in high definition. Their findings, published in *PNAS*, could help in guiding the development of therapeutics to fight norovirus infection.

The team found an unexpected mixture of different shell sizes and shapes. A smaller form consists of just 60 building blocks with 30 surface spikes placed farther apart. Larger shells were made out of 240 building blocks with 120 surface spikes that are lifted significantly above the base of the shell and form a two-layered architecture that could interact differently with human cells. It is the spikes on the shell that interact with the host, and the distance and orientation of the spikes varied across the different strains of noroviruses. This means each strain will interact differently with human cells and the way the antibodies bind is also going to be different. These variations are key to vaccine development.

Hidden Molecular Pocket Key to Treating Brain Injury


H. Furukawa

The ideal drug is one that only affects the exact cells and neurons it is designed to treat, without unwanted side effects. Professor Hiro Furukawa revealed a mechanism that could lead to this kind of long-sought specificity for treatments of strokes and seizures.

When the human brain is injured during a stroke, parts of the brain begin to acidify, and this leads to the rampant release of glutamate. The glutamate hits the NMDA receptor, causing it to fire—a lot. In a healthy brain, the NMDA (*N*-methyl-D-aspartate) receptor is responsible for controlling the flow of electrically charged atoms in and out of a neuron. The "firing" of these signals is crucial for learning and memory formation. However, overactive neurons or abnormal NMDA receptor activities have been observed in various neurological diseases and disorders, such as stroke, seizure, depression, and Alzheimer's disease.

Furukawa's team looked for a way to prevent overfiring NMDA receptors without affecting normal regions of the brain. Previous work had identified compounds, called the 93-series, suited to this purpose. Eager to join with the NMDA receptor in an acidic environment, these compounds down-regulate the receptor activity, even in the presence of glutamate, thereby preventing excessive neuronal firing.

However, the 93-series compounds sometimes cause the unwanted consequence of inhibiting the NMDA receptors in healthy parts of the brain. The findings of Furukawa and his colleagues that improve on the unique features of the 93-series were detailed in *Nature Communications.*

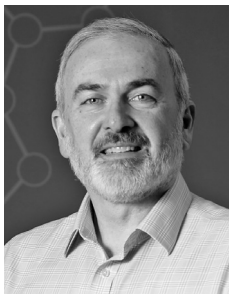
Research Faculty

Awards

Described as a "hub of breakthroughs," the 2019 *Nature Index* ranked CSHL the top institution for research output worldwide. Ambition and interdisciplinarity were notable characteristics of smaller institutions like CSHL, which proportionately outstripped larger institutions in the ranking.

The Laboratory's scientists were recognized individually by numerous honors throughout the year.

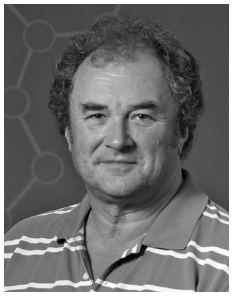
The Institute for Scientific Information at the Web of Science Group named seven researchers affiliated with CSHL among the scientists producing the top 1% of the most highly cited research in the world. Joining Professor Michael Wigler, one of the most extensively cited researchers of all time, were Tom Gingeras, Josh Huang, Dick McCombie, Michael Schatz, David Tuveson, and Doreen Ware, as well as affiliate Greg Hannon.



A. Krainer

Professor Adrian Krainer continued to receive honors for his work in RNA splicing and nusinersen (Spinraza®), a treatment for the neurodegenerative disease spinal muscular atrophy (SMA). He won the 2019 Breakthrough Prize in Life Sciences, the 2019 Peter Speiser Award, conferred by the Institute of Pharmaceutical Sciences of ETH Zürich, and the K-J. Zülch Prize from the Gertrud Reemtsma Foundation of the Max-Planck-Gesellschaft Society. Adrian was elected to the National Academy of Medicine.

The RNA Society named Adrian the recipient of the 2019 Lifetime Achievement Award. The RNA Society emerged from a group of scientists who, starting in 1982, met at CSHL for regular "RNA Processing" meetings. In 1993 the society was established formally, and although the annual members' meeting takes place elsewhere, an RNA Processing meeting is still held regularly at the Lab.



N. Tonks

Professor Nicholas Tonks was named a 2019 Fellow of the American Association for the Advancement of Science (AAAS). Nick was honored in the field of Pharmaceutical Sciences for his contributions to our understanding of signal transduction, through the discovery of protein tyrosine phosphatases and the characterization of their structure, regulation, and function.

Professor and Howard Hughes Medical Institute (HHMI) Investigator Zachary Lippman was a 2019 MacArthur Fellow. Often referred to as "genius grants," the fellowship provides exceptional individuals in a variety of fields with backing for their intellectual and professional pursuits. Zach's research focuses on the genes that determine when, where, and how many flowers are produced on a plant.

Professor and HHMI Investigator Rob Martienssen was awarded the 2019 Martin Gibbs Medal for his innovative work in the field of plant biology. The award is presented by the American Society of Plant Biology (ASPB) to "an individual who has pioneered advances that have served to establish new directions of investigation in the plant sciences."

Rob's current work focuses on investigating the epigenetic mechanisms of plants and understanding their role in gene regulation and inheritance. He is also an expert on transposable elements, or "jumping genes," studying how they regulate other genes and are in turn regulated during plant development. The Laboratory has a long history with the American Society of Plant Biology, with Charles Shull (who did plant biology work here in the early 1900s) having been part of the ASPB's founding body.

Professor Chris Vakoc was awarded the Paul Marks Prize for Cancer Research in recognition of his significant and ongoing contributions to the understanding of cancer. Presented through Memorial Sloan Kettering Cancer Center (MSKCC), the prize is awarded to up to three young scientists every two years. An expert in how genes are controlled and regulated, Chris studies how dysfunctional gene control can aid and even lead to cancer.

Z. Lippman

R. Martienssen

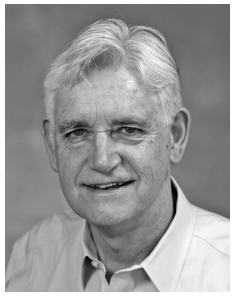
C. Vakoc

D. McCandlish

J. Lee

Assistant Professor David McCandlish was named a 2019 Sloan Research Fellow. David is a quantitative biologist who develops computational and mathematical tools to analyze genetic data. His lab focuses specifically on analyzing data from so-called "deep mutational scanning" experiments, which determine, for a single protein, the functional effects of thousands of mutations.

Assistant Professor Je H. Lee received the Chan Zuckerberg Initiative (CZI) Seed Networks for the Human Cell Atlas grant, to map gene expression and RNA–protein interactions throughout the formation of breast tissue. The Human Cell Atlas is a global, scientist-led effort to create a reference map of all cell types in the human body as a fundamental reference for biomedical research.



B. Stillman

I was humbled by the 2019 Canada Gairdner International Award for "pioneering research on the eukaryotic DNA replication cycles including initiation, regulation, and responses to DNA damage." It was rewarding to share this award with my collaborator Dr. John Diffley, Associate Director of the Francis Crick Institute, who was a former postdoctoral fellow in my lab.

The Gairdner Foundation's announcement states that "by describing the exact sequence of events involved in DNA replication, Stillman and Diffley have provided key insights into how our genome is duplicated and how this process is coordinated with many other essential cellular events, which have implications for understanding genome instability and tumor heterogeneity in cancer."

I was also elected as a Fellow of the American Association for Cancer Research (AACR) Academy.

New Hires/Promotions

We recruited three quantitative biologists to CSHL: Associate Professor Saket Navlakha; Assistant Professor Peter Koo; and CSHL Fellow Hannah Meyer.

CSHL Cancer Center Genetics and Genomics Program Leader, Chris Vakoc, was promoted to Professor.

Stephen Monez was recruited as Vice President, Chief Facilities Officer.

Education Highlights

Meetings & Courses Program

More than 7,200 participants from more than 50 countries attended meetings at CSHL this year. New meetings on Systems Immunology, Microbiome, and Zebrafish Neural Circuits and Behavior were added to the two-year cycle over which CSHL hosts 60 scientific meetings that span between three and five days.

S. Navlakha

P. Koo

H. Meyer

C. Vakoc

The Cold Spring Harbor Asia Program celebrated its 10th anniversary with a new partnership agreement signed by the Suzhou Industrial Park Administrative Committee that extends this program through 2028. In 2019, more than 3,300 participated in meetings at the Suzhou facilities. The next decade will see increased conference and course activities, as well as summer school programs, workshops, and smaller, invitation-only Banbury-style conferences.

At the Long Island campus, advanced scientific courses covered an array of topics in molecular biology, neurobiology, structural studies, and bioinformatics. Nearly 650 trainees, who included advanced graduate students, postdocs, and faculty, benefited from the contributions of the 700+ faculty.

The 84th Cold Spring Harbor Laboratory Symposium focused on RNA Control and Regulation, following previous symposia that have addressed different aspects of RNA biology, including the Symposia on Mechanisms in Transcription (1998), The Ribosome (2001), Epigenetics (2004), and Regulatory RNAs (2006).

Two of the three 2019 Nobel Prize winners in physiology or medicine, Bill Kaelin and Gregg Semenza, have both played active roles in a number of CSHL meetings, whereas the 2017 Nobel Prize winners Michael Rosbash and Michael Young jointly delivered the Seymour Benzer lecture at the 2019 Neurobiology of *Drosophila* meeting.

Banbury Center

Eighteen Banbury meetings spanned six thematic areas: cancer, neuroscience, technology, public health, plant biology, and science policy. The 475 global experts who participated in these meetings worked to develop strategies for emerging fields or innovate in existing fields, bridge divides across sectors, disciplines, and communities, and address challenging policy issues.

The Center was productive, with 11 articles based on Banbury meetings published in peer-reviewed journals, as well as a journal supplement. Among the publications, a Science Policy Forum article outlined recommendations to increase gender diversity in STEM research, based on 2018's Increasing Gender Diversity in the Biosciences meeting. Banbury continues to impact the Lyme disease field in 2019, with new FDA and CDC policy announcements on diagnostics in line with published recommendations from a 2016 meeting.

Deep conversation at a meeting about HIV at the Banbury Center

A formal initiative to collect information on longer-term outcomes and impact of the Center's program was initiated, with a survey of 2017 meeting attendees. Ninety-nine percent of respondents indicated that new knowledge they gained at Banbury informed their work and 63% developed new collaborations as a result. For 25% of respondents, the meeting led to a new grant proposal, and 53% indicated that the meeting informed a new grant proposal. Although policy issues were part of the objectives for only a handful of the polled meetings, 30% of respondents reported that a meeting informed their policy views, with 13% reporting that the meeting contributed to a change in policy.

Watson School of Biological Sciences

The 21st incoming class comprised four U.S. and four international students from Armenia, Mexico, China, and the United Kingdom. True to its mission to graduate students faster than students in comparable Ph.D.-granting institutions and position them to secure excellent jobs early in their careers, the program through 2019 counted 114 Ph.D. graduates. Thirty graduates had secured tenure track faculty positions. Twelve have been promoted to associate professor, and two are full professors. Our graduates have also moved into influential positions in administration, publishing, consulting, and industry.

Alumni Zach Lippman was awarded a MacArthur Foundation "Genius" award. Kristen Delevich was awarded a NARSAD Young Investigator Grant from the Brain and Behavior Foundation, and Nilgun Tasdemir was awarded a Pathway to Independence (K990/R00) Award from the National Institutes of Health (NIH).

Current students won prestigious fellowships, awards, and prizes, including the National Science Foundation Graduate Research Fellowship to Lyndsey Aguirre; the Boehringer Ingelheim Fonds Fellowship to Diogo Maia e Silva; and the Gilliam Fellowship for Advanced Study from the Howard Hughes Medical Institute to David Johnson. During the year, scientific papers published by current students of the School appeared in major journals, bringing the cumulative total of papers published by our students on their thesis research to more than 450.

A supplement to the program's NIH T32 training grant was funded in June, allowing for development of new course work and training modules related to career development. The new

WSBS entering class of 2019

curriculum is aimed at increasing student awareness and readiness for careers available to Ph.D.s; communication and negotiation skills and mentor/mentee relationships; and experiential learning in select career paths.

The 60th Undergraduate Research Program welcomed 18 undergraduates from the United States, China, and Ireland. The innovative Partners for the Future Program brought gifted local high school students to CSHL laboratories for hands-on research during their senior year.

DNA Learning Center

In October, the DNA Learning Center (DNALC) became a lead institution in the InnovATE*BIO* National Biotechnology Education Center funded by the National Science Foundation's Advanced Technological Education (ATE) program. With a goal of workforce competitiveness, the program is focused on two-year colleges. The project is administered from Austin Community College, and the leadership team includes Madison College, Forsyth Technical Community College, Finger Lakes Community College, and the Bay Area Biotechnology Education Community. The DNALC's role is to develop a New York City Genomics hub to foster innovative labs and to support course-based student research at two-year colleges—including DNA barcoding and meta-barcoding.

Furthering this initiative is the announcement that CSHL signed a lease agreement to open the DNA Learning Center NYC at CityTech in Brooklyn, New York. Hosted by the New York City College of Technology (CityTech), programming at this facility builds on CSHL's initial foray into NYC through the Harlem DNA Learning Center established in 2008. The Brooklyn location is an 18,000-square-foot space that will be easily accessible to students and teachers in Brooklyn and the entire city of New York. In addition to programs for middle and high school students and teachers, the partnership with CityTech will develop research experiences and new curriculum for CityTech's two- and four-year degree programs.

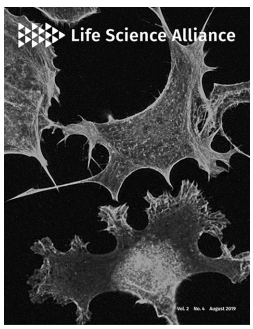
In collaboration with Regeneron Pharmaceuticals, Inc., CSHL launched the Regeneron DNALC to serve the Hudson Valley. The new 4,700-square-foot center is located on Regeneron's Sleepy Hollow campus in Westchester County, New York. The interactive

CityTech interior

educational center is equipped with two state-of-the-art teaching labs to host local middle and high school field trips during the academic year, summer camps, and semester or year-long research projects.

During the academic year 20,358 students conducted labs at the Dolan DNA Learning Center, DNALC West, Harlem DNA Lab, Regeneron DNALC, and a temporary lab at CityTech; whereas 1,157 students attended week-long summer camps and 315 participated in research using DNA barcodes. An additional 7,628 students conducted in-school labs led by DNALC staff, and 1,758 used footlocker kits. Also this year, 5,224,126 visitors accessed DNALC's suite of multimedia resources online, including 3,749,711 visits to DNALC websites, 883,944 views of YouTube videos, and 590,471 downloads of smartphone/tablet apps, the *3D Brain, Weed to Wonder,* and *Gene Screen.*

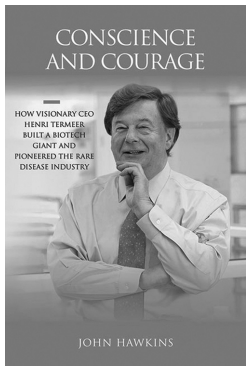
Cold Spring Harbor Laboratory Press



The open-access journal *Life Science Alliance*

The six research and three review journals published by the Press are the largest component of its publishing program. All of the review journals expanded their audience in 2019 and *Genes & Development, Genome Research*, and *RNA* remained prominent in their fields. The transition of the Laboratory's journal publishing program to an open-access model was signaled with the 2016 launch of the precision medicine journal *Cold Spring Harbor Molecular Case Studies*, which continued to gain submissions and readership in its fourth year. The open access journal *Life Science Alliance* was launched in 2018, published jointly by CSHL, the European Molecular Biology Organization, and Rockefeller University. This journal published 179 new articles in 2019, and monthly usage of its content grew >300% during the year.

Fewer print books are being published as the content typical of monographs and laboratory manuals is now delivered primarily online. *Conscience and Courage: How Visionary CEO Henri Termeer Built a Biotech Giant and Pioneered the Rare Disease Industry*, by John Hawkins, was a bestseller among the 12 new books published in 2019.



The cover of *Conscience and Courage*

Most Press backlist books are now available in both print and e-book formats and direct sales from the Press website are close to those of the major online retailers. The mission of the Press remains helping scientists succeed, while enhancing the Laboratory's reputation, reach, and financial condition.

Preprints in Biology and Medicine

bioRχiv
THE PREPRINT SERVER FOR BIOLOGY

medRχiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

A preprint is a research manuscript its authors first distribute via a dedicated server platform. Launched in 2013, the Laboratory's preprint server for life sciences, bioRxiv, made 68,800 papers freely available by the end of 2019 and attracted more than 4.7 million page views per month.

Inspired by bioRxiv's momentum, a preprint server for health sciences, medRxiv, was launched in June 2019 by the Laboratory in a management partnership with Yale University and BMJ, the global health information provider. By December medRxiv had posted more than 900 manuscripts and was receiving close to 1 million page views and downloads each month.

A preprint permits open community assessment of new research, but the formal peer review, endorsement, and publication of that work by research journals remains important. As part of a growing wave of experiments in how peer review is done, bioRxiv launched Transparent Review in Preprints (TRiP) in September 2019, bringing to readers of a preprint the reviews of the research commissioned by journals and other organizations.

By the end of 2019, the Laboratory's preprint platforms had distributed new work from investigators in more than 140 countries and it was evident that this new form of communication is transforming how biomedical research is conducted worldwide.

Board of Trustees

Under the leadership of Chairman Marilyn Simons, Ph.D., the CSHL Board of Trustees elected four new trustees: Christine Anderson, Lyon Polk, Laura Slatkin, and Diana Taylor.

The Double Helix Medals Dinner (DHMD) honoring Boomer Esiason and Nancy Wexler, Ph.D., raised more than $4 million. Columbia University professor and president of the Hereditary Disease Foundation, Wexler is known for her scientific contributions on Huntington's disease and involvement in public policy, individual counseling, genetic research, and federal health administration. Former NFL quarterback Esiason advocates for cystic fibrosis research through the Boomer Esiason Foundation, a dynamic partnership of leaders in the medical and business communities, to heighten awareness, education, and quality of life for those affected by cystic fibrosis.

The dinner was chaired by Jamie Nicholls and Fran Biondi, Marilyn and Jim Simons, Teresa and Bob Lindsay, Janet and Frank DellaFera, Jenny and Jeff Kelter, and Danielle and Paul Taubman.


C. Anderson


L. Polk


L. Slatkin


D. Taylor

Since the first DHMD honored Muhammad Ali in 2006, the event has raised more than $40 million for the Laboratory's biological research and education programs.

Marilyn and Jim Simons made a significant pledge to support the future expansion of campus facilities, including housing for visiting scientists and additional lab space for neuroscience and quantitative biology research. Schmidt Futures pledged support to seed an Artificial Intelligence Fellows Program. Jenny and Jeff Kelter named a fellow in the graduate school.

Library and Archives

With a pledge from BGI Group, the global genomics leader headquartered in Shenzhen, China, the BGI Nobel Laureates Archives was established. It comprises all of the current and future personal collections of Nobel laureates held by the CSHL Archives and includes Sydney Brenner, Francis Crick, Walter Gilbert, Carol Greider, Alfred Hershey, Barbara McClintock, Hermann Muller, Richard Roberts, and James Watson.

BGI shares the roots of human genetics history with CSHL, starting from the Human Genome Project (HGP). BGI, originally called the Beijing Genomics Institute, grew out of the vision of its founders to participate in the Human Genome Project, and they led China's contribution to that international effort. The new archive is an asset for the global community of genetics. BGI and its employees who contributed to this pledge strive to join the effort of CSHL to protect the heritage and to digitize the archives so that this resource is more accessible to mankind.

The Archives' History of Science annual meeting was titled Yeast Research: Origins, Insights, and Breakthroughs. Other events included a Special Lecture by Professor Rob Martienssen called Barbara McClintock's Controlling Elements Then and Now, and two Meet the Author events featuring 2009 Nobel laureate Venki Ramakrishnan and Anna Marie Skalka, Professor Emerita at Fox Chase Cancer Center.

Business Development & Technology Transfer

2019 followed the banner year of 2018 that was dominated by the monetizing of the 2016 FDA-approved spinal muscular atrophy drug Spinraza®. The Business Development & Technology

H. Yang, B. Stillman, L. Pollock

Transfer team focused on building multiple industry relationships that represent significant and long-term value to CSHL.

The team increased licensing and equity revenue to $4 million, leveraging Krainer lab initiatives to expand patent reimbursement costs and liquidate stock from the CSHL spin-out company, Stoke Therapeutics, following a successful IPO. $400,000 in sponsored research funding was received under agreements negotiated and managed by this team.

Positioning around the business of "Innovation," the department worked to partner scientists with companies and investors to bring CSHL discoveries to the public domain through intellectual property and know-how licensing, industry (as well as academic) collaborative research, and new ventures.

The team is developing high-quality relationships between faculty and the best partner companies for their field. This high-level engagement supports the establishment of sponsored research agreements with multiple start-up companies and a large pipeline of opportunity with increasing numbers of faculty involved in translational work.

Infrastructure

New York State Governor Andrew Cuomo helped open the newly renovated Demerec Laboratory in the fall. "It's good for the economy, but also [this is research] that I believe will improve the quality of life for thousands and thousands of people. I believe this work will save lives," Cuomo said during his visit. Home to four Nobel laureates, this building has been historically central to genetics research in New York and the world. New research in the building will focus on a holistic approach to treating cancer and the disease's impact on the entire body.

"This renovation allows us to really think about where the Lab will take things next," said Stillman. "It will have, I hope, a global impact on the research community, especially in the biomedical sciences."

Other significant projects this year included:

- *Marks Annex construction*. This included an additional postdoc office space, two conference rooms, and collaboration space with expected completion by mid-2020.

Governor A. Cuomo and B. Stillman walking in Demerec Laboratory, looking at images of famous scientists who had worked in that building.

An Open House event attracts participants to experiment for themselves.

- *Woodbury Genome Center Greenhouse construction*. This included an additional 2,500 square feet of greenhouse space with expected completion mid-2020.
- *DNA Learning Center at CUNY CityTech in Brooklyn, New York*. Planned construction includes 17,500 square feet of teaching facilities in the CityTech Pearl Building with construction activities to begin early 2020 and expected completion by spring 2021.
- *Airslie House renovation*. Construction activities continued with expected completion summer 2020.

The Laboratory continued its program of modernizing and improving the heating, ventilation, air conditioning, electrical, and plumbing systems throughout the campus.

Community Outreach

In June, CSHL welcomed more than 650 neighbors and friends to an Open House event that showcased the many different facets of the Lab and what happens on our campuses every day. Nearly 80 CSHL staff, graduate students, postdocs, and faculty helped visitors explore the campus and learn about our innovative research and education programs.

Scientists shared the latest from their laboratories about DNA, plant biology, cancer research, neuroscience, and quantitative biology. At numerous experimentation stations, scientists showed off corn samples, allowed peeks into microscopes, and gave lessons on how to extract DNA. There were also short talks on topics that ranged from understanding the immune system, tackling pancreatic cancer, and developing biofuels, to how the Banbury Center "think tank" has helped advance science policy.

A team of 18 CSHL graduate students guided 78 public tours throughout the year. More than 1,500 visitors participated in these events. Graduate students and instructors from the DNA Learning Center participated in events to engage with local elementary school children and support local school science fairs and science demonstrations.

CSHL's Public Affairs Department managed these outreach events and continued the annual science lecture series at Grace Auditorium. This team also organized more informal events that bring our science to the general public in other locations throughout the community.

A. Solomon and M. Wigler discuss *Far from the Tree*.

CSHL Public Presentations

January 19: Screening and discussion at Cinema Arts Centre in Huntington Co.; *Far from the Tree*; Panelists: **Michael Wigler, Ph.D.,** professor, CSHL; **Andrew Solomon,** writer; co-presented by Cold Spring Harbor Laboratory and Cinema Arts Centre as a Science on Screen event.

April 11: Lecture at Port Washington Public Library; Pancreatic Cancer: Advances in Research; **Lindsey Baker, Ph.D.,** CSHL research investigator; co-presented by Cold Spring Harbor Laboratory and the Lustgarten Foundation.

April 17: Public lecture, Seeing with Sequencing; **Molly Gale Hammell, Ph.D.,** associate professor, CSHL; **Justin Kinney, Ph.D.,** assistant professor, CSHL; **David McCandlish, Ph.D.**, assistant professor, CSHL.

April 24: *Cocktails & Chromosomes* at Six Harbors Brewing Co.; **Ullas Pedmale, Ph.D.,** assistant professor, CSHL.

May 29: Screening and discussion at Cinema Arts Centre in Huntington; *Iceman*; Panelists: **Lindsay Barone, Ph.D.** and **Elna Carrasco-Gottlieb,** DNA Learning Center; co-presented by Cold Spring Harbor Laboratory and Cinema Arts Centre as a Science on Screen event.

June 24: Public lecture, Diet and Disease: Exploring the relationship between nutrition and cancer; **Semir Beyaz, Ph.D.,** CSHL fellow; **Jamie Kane, M.D.,** director, Center for Weight Management, Northwell Health, assistant professor, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell; co-sponsored by CSHL, US Trust, Northwell Health, and St. Johnland Nursing Center.

July 17: *Cocktails & Chromosomes* at Six Harbors Brewing Co.; **Camila dos Santos, Ph.D.**, assistant professor, CSHL.

October 6: Public lecture, Diversity, Ethnicity and Cancer; 2019 Lorraine Grace lectureship on societal issues of biomedical research, presented as part of the ongoing Roy J. Zuckerberg community engagement series from CSHL's NCI-Designated Cancer Center; **Olufunmilayo I. Olopade, M.D., F.A.C.P.,** Walter L. Palmer Distinguished Service Professor of Medicine and Human Genetics, director, Center for Clinical Cancer Genetics & Global Health, University of Chicago Medicine.

October 10: *Cocktails & Chromosomes* at Six Harbors Brewing Co.; **Tobias Janowitz, M.D., Ph.D.**, assistant professor, CSHL.

October 28: Public lecture, Food and Climate—the Way Forward; Introduction: **Bruce Stillman, Ph.D.,** CSHL president and chief executive officer; Speaker: **Katy Kinsolving**, president of the C-Change Conversations; Panelists: **Rebecca Benner**, director of Conservation and Science for the Nature Conservancy; **Peter Lehner**, director of Earthjustice's Sustainable Food & Farming Program; **Doreen Ware, Ph.D.,** molecular biologist with the USDA Agricultural Research Service (ARS) and CSHL adjunct professor; presented by Cold Spring Harbor Laboratory and North

Shore Land Alliance together with North Country Garden Club, St. John's Church (Cold Spring Harbor), the Nature Conservancy (Long Island chapter), and Three Harbors Garden Club.

November 13: *Cocktails & Chromosomes* at Six Harbors Brewing Co.; **Lloyd Trotman, Ph.D.**, professor, CSHL.

Zlatomir Fung (credit, Matt Dine)

CSHL Public Concerts

April 5: Nathan Lee, piano
April 26: Matthew Graybil, piano
May 3: Tanya Bannister, piano
August 23: Jiayin Shen and Igor Lovchinsky, piano duo
September 13: Horszowski Trio
September 27: Hanzhi Wang, accordion
November 8: Zlatomir Fung, cello

Looking Forward

CSHL named a Top Workplace

CSHL was proud to be named again by *Newsday* as one of Long Island's Top Workplaces. The anonymous employee surveys of employers across Long Island were analyzed by a third party. As part of the large company category, those with more than 500 employees, the Lab shared the honor with only 12 other institutions. This is CSHL's second year winning this prestigious award. Thank you to our faculty, students and employees for making CSHL a great place to work and to all of you who contribute to the success of this institution. With your support, we will continue to advance biology and genetics to benefit mankind.

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