Highlights of the Year

Research

Hundreds of scientists working in Cold Spring Harbor Laboratory's 50-plus laboratory groups contributed to research that in 2018 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 the year's important findings.

Doubling the Number of Grains in Sorghum

D. Ware

A simple genetic modification can triple the grain number of sorghum, a drought-tolerant plant that is an important source of food, animal feed, and biofuel. By lowering the level of a key hormone, the team (led by Doreen Ware in collaboration with her USDA colleague Zhangou Xin of Lubbock, Texas) generated more flowers and more seeds.

Sorghum's grains are produced in clusters of flowers that develop from a branched structure at the top of the plant called a panicle. Each panicle can produce hundreds of flowers. There are two types of flowers, and usually only one of these, known as the sessile spikelet, is fertile. The other flower type, called pedicellate spikelets, does not make seeds. In modified plants, however, *both* sessile and pedicellate spikelets produced seeds, doubling each plant's grain number.

By sequencing the genomes of the modified plants, Ware's team found key mutations affected a gene that regulates hormone production. Plants carrying the mutation produce abnormally low levels of a development-regulating hormone called jasmonic acid, particularly during flower development. Through subsequent experiments, the team learned that jasmonic acid prevents pedicellate spikelets from producing seeds.

The team now wants to understand whether the strategy can be applied to increase grain production in related plants that are vital in the global food supply, such as rice, corn, and wheat.

Unique Communication Strategy in Pathway Controlling Plant Growth

D. Jackson

CSHL plant geneticists identified a receptor protein on stem cells involved in plant development that can issue different instructions about how to grow depending on what peptide activates it. The findings by David Jackson and colleagues have implications for efforts to boost yields of food crops such as corn and rice.

Plant growth and development depend on structures called meristems—reservoirs that contain stem cells. When prompted by peptide signals, stem cells develop into any of the plant's organs—roots, leaves, or flowers, for example. These signals work like a key (the peptide) fitting into a lock (the receptor protein) on the surface of a cell. The lock opens, stimulating a messenger inside the cell. The messenger carries instructions for the cell to grow into a leaf or flower cell or even stop growing altogether. Conventionally, one or more peptides fit into each receptor to stimulate a single type of messenger.

In 2001, Jackson and colleagues discovered that a receptor protein called FEA2 can stimulate one of two distinct messengers into the cell depending on which of two peptides, ZmCLE7 or ZmFCP1, switches it on. Receptors such as FEA2 that stimulate more than one messenger are rare. This is the first one discovered that plays a role in crop production.

Jackson and his team believe that FEA2 is bound to two different co-receptors, each of which acts as the "lock" for one of the two peptide "keys." Future research will explore how the two different peptide signals are translated by FEA2 into distinct messenger outputs.

A Way to Make Prostate Cancer Cells Run Out of Energy and Die

Cells lacking the tumor-suppressor protein PTEN—a feature of many cancers—have been determined by Lloyd Trotman to be vulnerable to drugs that impair their energy-producing mitochondria. Unlike normal cells, cells without PTEN seem driven to preserve their mitochondria at all costs. Trotman and colleagues found that when such cells are treated with certain mitochondrial inhibitors, they consume vast quantities of glucose to fuel these efforts. As a result, they quickly run out of energy and die.

L. Trotman

Some mitochondrial inhibitors, including the diabetes medication metformin, are being tested for their ability to treat cancer. Trotman's findings suggest that such drugs have the potential to eliminate cancer cells at doses that leave healthy cells intact, particularly in cells that have compromised PTEN function. "The hope is that carefully timed administration of these drugs can generate a much better window of selective killing," Trotman says.

Two related compounds emerged from a screen performed by the team. Both killed cells missing PTEN and another tumor suppressor, p53. Loss of these together is common among men with advanced prostate cancer that is also highly metastatic, a particularly lethal form of prostate cancer.

The two drugs had little effect on nearly identical cells with functional PTEN. One, rotenone, is a known mitochondrial inhibitor. Trotman established that the second compound, deguelin, shuts down mitochondrial function just as well in cells with PTEN as it does in cells that lack it. This raised the question of why normal cells were able to tolerate the toxic compound.

The answer has to do with how cells use glucose. Cells without PTEN take in glucose from their environment to generate the energy-rich molecule ATP, which they import into mitochondria to keep them intact. But, mitochondria are supposed to *generate* ATP for the rest of the cell, not consume it. For the cells lacking PTEN, unless there is an endless supply of glucose, they quickly use up the sugar and die.

All cells need glucose, but cells with an unusual need for it, like cancer cells lacking PTEN, are especially vulnerable to its availability. This means it could be critical to administer mitochondrial inhibitors to cancer patients when their blood sugar is low, Trotman says.

From Many Mice, Unexpected Variety in Decision-Making Strategies

When it comes to sample sizes in experiments to understand decision-making, a CSHL team found that testing more subjects in more trials is not only better, but necessary, to truly grasp what an individual is thinking.

Anne Churchland and colleagues presented about three dozen mice with a task: Watch blinking lights and determine the frequency of the flashing, or stimulus. "If they are correct, the mice learn that if it's a low-rate stimulus they should move to the left port to get a reward; and if it's high-rate, they go the other direction to get the reward," the neuroscientist explains.

A. Churchland

The scientists assumed that the rate of the flash was all the mice would pay attention to, and set up the experiment to ensure that the mice had no other source of information to distract them. But, unexpectedly they found that some mice simply estimated the brightness of the complete flashing experience.

"If you think about it, a high-rate stimulus is 15 flashes per second. The overall amount of photons emitted will be higher than if it's a low-rate stimulus, flashing seven times per second. So, some mice figured out that they don't actually have to count the flashes," said Churchland. "The mice could just measure the total number of photons coming from the LED panels that we used. They found this extra piece of information that we hadn't realized was there."

If the researchers had just looked at a few mice in this experiment, they would have missed the fact that some of them were more clever. The team included this finding in their equations and set themselves up to learn more about each individual mouse's ability to deduce.

"If we understand why an individual is making a decision (i.e., what they're considering), we can better understand the mechanisms in the brain supporting that decision," Churchland said. "It's critical to thoroughly understand what the animal's strategy is and to be in a position to distinguish different decision-making strategies."

How Pancreatic Cancer Spreads after Surgery

Surgery is usually not an option for pancreatic cancer patients whose primary tumor has metastasized. But doctors have been puzzled by the poor outcome of patients whose tumor seems confined to the pancreas at the time of diagnosis and thus qualify for surgery. In many such patients, the liver appears cancer-free. Yet within 2 years, most of these patients develop lethal metastatic cancer, often in the liver.

D. Fearon

Doug Fearon discovered how the cancer spreads in patients whose tumor is successfully removed. After surgery, patients experience a 2-week period during which their immune system is depleted as a result of a surge in postoperative stress hormone (cortisol) levels. With killer T-cell levels sagging, isolated, dormant cancer cells that have already traveled to the liver via the bloodstream begin to grow or metastasize.

This postoperative period, suggests Fearon, "offers a window during which efforts might be made to keep cortisol levels down and T cells strong so the patient's own immune system can kill the cancer cells that have made their way to the liver but until this point have been dormant."

Fearon's team explains that dormant cancer cells are already in the liver well before patients have their primary tumor removed. They are carried there by the bloodstream, having been shed by the primary tumor. The immune system can kill most—but not the dormant—non-growing cancer cells that are deposited in the liver.

The immune system seeks and destroys cancer cells by sensing proteins called MHC I present on the outer membrane of the cancer cells. Fearon's team found that the cancer cells that have been lying dormant in the liver of pancreatic cancer patients do not express these proteins, so killer T cells cannot find them. In situations such as postoperative surgical stress, in which T cells in the liver are depleted, the dormant cancer cells reexpress MHC I and begin to divide, becoming seeds of metastatic lesions. Even though the MCH I molecule is expressed, the stress-induced cortisol blocks the T-cell response, allowing the growing metastatic cells to escape T-cell killing.

How a Sleeping Cancer Awakens and Metastasizes

Even after successful cancer treatment, dormant, nondividing cancer cells that previously detached from the original tumor may exist elsewhere in the body. If awakened, these cells can grow into metastatic tumors. Studying metastasis to the lungs, Mikala Egeblad's laboratory identified signals accompanying inflammation that can awaken dormant cancer cells.

M. Egeblad

The team demonstrated that sustained lung inflammation, including that caused by tobacco smoke exposure, can cause dormant breast and prostate cancer cells that have traveled to the lungs to awaken and metastasize in the lungs.

With colleagues, they demonstrated a way to block the signal that awakened the dormant cancer cells, a concept that could prevent cancer recurrence. The team showed that sustained lung inflammation induced common white blood cells called neutrophils to awaken nearby dormant cancer cells.

Neutrophils normally kill invaders like bacteria and yeast. They can expel their DNA into the space beyond the cell membrane. Laced with toxic enzymes, this expelled DNA forms net-like traps (called neutrophil extracellular traps, or NETs) that can kill a pathogen.

Egeblad showed that sustained lung inflammation causes the formation of NETs in the area around dormant cancer cells. Two enzymes in the NETs interact with a protein in tissue called laminin. In sequence, the enzymes make cuts in laminin proteins and change their shape, exposing a new surface (called an epitope).

When recognized by dormant cancer cells nearby, the epitope spurs signaling that awakens the cancer cells. The Egeblad team created an antibody to block the epitope, and, in mice, this prevented the reawakening of dormant cancer cells. Work has begun to optimize the antibody, with the hope of conducting trials in humans.

Organoid Profiling Personalizes Treatments for Pancreatic Cancer

D. Tuveson

A team of researchers led by CSHL Cancer Center Director David Tuveson demonstrated that patient-derived organoids, hollow spheres of cells cultured directly from a patient's tumor, can quickly and accurately predict how patients with pancreatic cancer respond to a variety of treatments.

Pancreatic cancer is one of the deadliest cancers. Currently, surgical removal of the cancerous tissue is the only effective treatment—but because the disease progresses so quickly, only 15% of patients are eligible for the procedure. Surgery-ineligible patients can be treated with chemotherapy, but patient response is highly varied, and there is no good method to determine which treatment is best for any given patient.

For several years, the Tuveson laboratory has been honing organoid technology. Taking only 3–6 weeks to grow, a major advantage of organoids is that they can be derived from tumors using tiny needle biopsies. Tuveson's team grew organoids from 66 pancreatic cancer patients and tested the sensitivity of each sample to five standard-of-care chemotherapy drugs. The team also measured the gene expression patterns in these organoids and compared the gene expression patterns to the drug sensitivity of the five different chemotherapies. They found that three "signatures" of gene activity in the organoids correctly identified patients who had responded well to these drugs, using tumor samples from several Canadian clinical trials. "The signatures are promising and may enable physicians to choose the best initial chemotherapy treatment for pancreatic cancer patients," Tuveson says. Tuveson also said that such "pharmaco-typing" approaches may apply to other cancer types.

Tuveson and his team plan to further refine the gene signatures and to test in prospective clinical trials the ability of these signatures found in organoids to predict the responses of pancreatic cancer patients.

A New Type of Lung Cancer

C. Vakoc

Researchers discovered a new kind of small-cell lung cancer (SCLC), paving the way for developing personalized medicine approaches to target it. About 10%–15% of all lung cancers are SCLC, a cancer without a specific treatment that often spreads early.

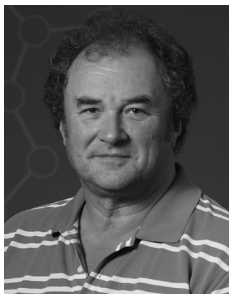
Analysis of gene activity in human SCLC tumors revealed an unexpected activity pattern in ~20% of samples. Christopher Vakoc and his team found a paucity of neuroendocrine markers in pulmonary neuroendocrine cells, a cell type thought to be the source of SCLC.

To further characterize this minority of cells, Vakoc and colleagues used a method they developed in 2015 that employs the gene-editing tool CRISPR to screen for specific proteins that are critical to the growth of various human cancer cell lines. They found that a transcription factor called POU2F3 is expressed exclusively in the minority of

SCLC tumors with low levels of neuroendocrine markers. Developing drugs that specifically target the function of POU2F3 may be particularly effective in the subset of patients with tumors that express high levels of this transcription factor.

Vakoc's team is now looking to do preclinical tests in mice to test compounds that target POU2F3.

Toward an Improved Wilson's Disease Drug



N. Tonks

In collaboration with DepYmed Inc., a CSHL spinout company, Nicholas Tonks and his team conducted promising preclinical experiments on a compound to treat Wilson's disease and other disorders in which levels of copper in the body are elevated.

Wilson's disease, affecting 1 in 30,000 people, is a severe inherited disorder that leads to profound liver and neurological damage. It is caused by mutations in a gene that encodes an enzyme critical in the excretion of excess copper from cells and organs. Copper is obtained mainly through the diet. Although essential in bodily function, it can be toxic when it accumulates. Normally, amounts of copper are precisely regulated both at the cellular level and in the body as a whole. In Wilson's patients, abnormal copper buildup begins in the liver. Copper toxicity can lead to liver enlargement, hepatitis, cirrhosis, and liver failure.

The team's research confirms that DPM-1001, a small molecule, robustly reduces copper levels in cells grown in culture that were sampled from Wilson's disease patients, as well as systemically in a mouse model of the disease.

The team showed that DPM-1001 could be taken as a pill, and is "exquisitely specific" for copper. Current de-coppering agents tend to affect levels of other metals in addition to copper—an undesirable feature in a drug for an illness like Wilson's.

In a mouse model of Wilson's disease, DPM-1001 ameliorated associated liver complications. This was accompanied by dramatic lowering of tissue copper levels and reduced disease symptoms. Optimization work on the compound continues in his laboratory in collaboration with DepYmed Inc.

Using CRISPR to Bring Orphan Crops to Market

Z. Lippman

Most people have never tasted a groundcherry—the small, sweet relative of the tomato. That's because the groundcherry plant, with long, straggly branches and sporadically ripening fruit, is unsuitable for large-scale agriculture. Zach Lippman used the gene-editing tool CRISPR to engineer groundcherries that maintain compact, manageable stems and that produce larger, more abundant fruit.

Lippman and colleagues described the effects of changes to three groundcherry genes. One change reins in production of a hormone that regulates flowering, making plants more compact and producing fruit in clusters. A change to another flowering hormone leads to denser fruit production: Plants with a CRISPR-generated mutation in this gene produced up to 50% more fruit than the unmodified plant. The third change boosts the number of seedy sections within each fruit, increasing its overall size.

The team is working on other aspects of the plant to make the groundcherry practical for large-scale production. The current success demonstrates that it is possible. In less than 2 years, they achieved improvements that would have taken far longer using traditional breeding practices. The implications are much broader. With gene editing, other wild plants or orphan crops may be brought into agricultural production.

Research Faculty

Awards

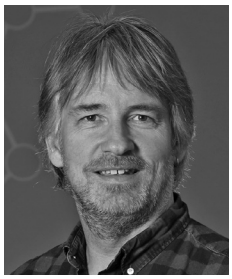
Professor Adrian Krainer was awarded the prestigious Breakthrough Prize at the celebrity-studded, televised ceremony known as the "Oscars of Science." The November ceremony included

A. Krainer

Emma Larson, a little girl who participated in the clinical trial to test the lifesaving spinal muscular atrophy (SMA) treatment drug that Krainer co-developed. Krainer received numerous additional accolades throughout the year for his ability to dive deeply into the basic biology of RNA splicing and then work collaboratively with industry partners to apply this knowledge to develop a drug.

Krainer came to the Lab more than 30 years ago, as the first CSHL Fellow. He had just received his Ph.D. at Harvard, and CSHL gave him the extraordinary opportunity to run his own, curiosity-driven lab. Programs to support early-career scientists in pursuing independent research continue here today.

In addition to winning the 2018 Breakthrough Prize, Krainer was named a National Academy of Inventors (NAI) 2018 Fellow, honored for his work on Spinraza®, the first FDA-approved treatment for SMA. NAI Fellows are nominated by their peers; those chosen for the honor demonstrate a highly prolific spirit of innovation in creating or facilitating outstanding inventions that have made a tangible impact on the quality of life, economic development, and welfare of society.



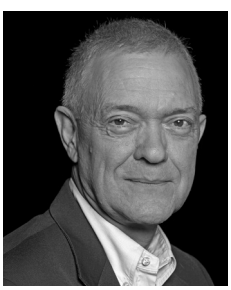
D. Jackson

CSHL had two American Association for the Advancement of Science (AAAS) 2018 Fellows. Professor David Jackson was honored in the field of Agriculture, Food and Renewable Resources for his discoveries of the genes and signals that regulate stem cell behavior in plants, thereby affecting plant architecture and yield.

In the field of Biological Sciences, Jan A. Witkowski, Watson School of Biological Sciences professor, was awarded for his seminal role in advancing science through his leadership of the Banbury Center. CSHL's think tank for science, Banbury Center is recognized by AAAS for holding discussion meetings that review key issues in biology and medicine.

Professor Leemor Joshua-Tor was honored by the American Society for Biochemistry and Molecular Biology's 2018 Mildred Cohn Award in Biological Chemistry. The award is named for the pioneering biochemist who developed powerful techniques for understanding how molecules behave in the body. The highly prestigious Cohn Award recognizes innovative scientists who have made substantial advances in understanding biological chemistry. Accepting the award, her lecture focused on the structure of a molecule that enables DNA to be accurately replicated as each new cell is born. It is one of countless projects that Joshua-Tor has tackled since joining CSHL's faculty in 1995.

Professor Rob Martienssen received the 2018 Barbara McClintock Prize for Plant Genetics and Genome Studies. The Barbara McClintock Prize for Plant Genetics and Genome Studies was created to memorialize the contributions of Dr. McClintock. Her 1983 Nobel Prize in Physiology or Medicine was awarded for her discovery and characterization of transposable genetic elements that she determined could move within the genome. The McClintock prize recognizes the most outstanding plant geneticists of the present era.



J. Witkowski

L. Joshua-Tor

R. Martienssen

Martienssen was recognized for his pioneering contributions to epigenetic mechanisms of gene regulation and inheritance; his stellar work with transposons, DNA methylation, and histone modification, which has linked these with chromatin remodeling and RNA interference; his efforts revealing unifying mechanisms that underlie transcriptional and posttranscriptional silencing; demonstrating the existence of plant cell type–specific small RNAs and their capacity to alter imprinting by moving to adjacent cell types; and bringing diverse approaches to bear on identifying many genes that control classical genetic traits.

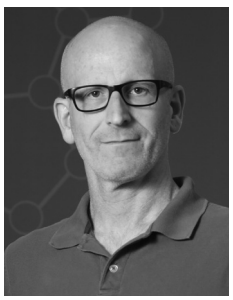
Professor Zachary Lippman was selected as a National Finalist in Life Sciences for the 2018 Blavatnik National Awards. The Blavatnik National Awards honor outstanding scientists under the age of 42 in the fields of Life Sciences, Chemistry, and Physical Sciences & Engineering. Lippman's research focuses on the genes that determine when, where, and how many flowers are produced on a plant, using tomatoes as a model system. Employing a combination of genetic, genomic, and molecular approaches, his team is developing new strategies for improving crop yields.

Blavatnik Award

Professor Anthony Zador was named a Gill Symposium Transformative Investigator for his work on MAPseq. The prize honors researchers who have made exceptional contributions to cellular or molecular neuroscience. MAPseq (multiplexed analysis of projections by sequencing) is a revolutionary brain-mapping method developed by Zador and his team. The tool barcodes thousands of neurons and determines their wiring patterns at single-neuron resolution.

Professor Nicholas Tonks was awarded the American Society for Biochemistry and Molecular Biology's (ASBMB) 2019 Earl and Thressa Stadtman Distinguished Scientist Award. Tonks' research has largely focused on the protein tyrosine phosphatase (PTP) family of enzymes, the "inaugural member" of which, PTP1B, he discovered in the late 1980s. In recent years, Tonks has obtained promising results aimed at devising new therapeutic strategies for diseases such as breast cancer, diabetes, Parkinson's, and Alzheimer's. This award, given to established scientists for their outstanding achievements in basic research, is issued once every two years.

Associate Professor Molly Hammell was awarded the Chan Zuckerberg Initiative (CZI) Ben Barres Early Career Acceleration Award for her proposed work on amyotrophic lateral sclerosis, better known as ALS or Lou Gehrig's disease. Hammell proposes to develop machine-learning software that would systematically identify genetic factors and molecular mechanisms that lead to motor neuron death. She will focus on transposable elements—viral-like genomic parasites that normally lie dormant in the genome—that are implicated in multiple diseases, including ALS. The award is a part of CZI's Neurodegeneration Challenge Network, which connects researchers who are studying neurodegenerative diseases and encourages a cross-disease perspective.


A. Zador


N. Tonks


M. Hammell

F. Albeanu and
A. Koulakov

M. Egeblad receiving the Suffrage
Science award

Associate Professor Florin Albeanu and Professor Alexei Koulakov received the National Institutes of Health (NIH) Director's Transformative Research Award for an innovative neuroscience research project on the olfactory system, one of the basic senses that is still quite mysterious. The project will study how the brain interprets odors, an aspect of neuronal processing. Together, Albeanu and Koulakov are building a general framework that will help standardize the study of olfactory receptors and how they broadcast odor-related information brain-wide. By gathering data in the Albeanu laboratory and applying mathematical methods used in artificial intelligence in the Koulakov laboratory, they hope to be able to predict olfactory "rules" based on the chemical structure of the odor. The NIH Director's Transformative Research Award provides funding for innovative research that is considered "high-risk" but has the potential to create or overturn fundamental paradigms of science.

Associate Professor Mikala Egeblad was honored with a Suffrage Science award at the Academy of Medical Sciences, London. The award, in the form of heirloom jewelry, honors women in science with the aim of encouraging more women to enter science, stick with it, and reach senior leadership roles. Rather than having committees select the winners, each winner selects who will get the heirloom jewelry next. Egeblad's cancer research laboratory focuses on understanding the network of immune cells, blood vessels, chemical signals, and support structures that make up what is known as the tumor microenvironment.

T. Engel

Assistant Professor Tatiana Engel is helping build computational tools for data collected specifically from the brain. She was awarded a Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative grant from the National Institutes of Health. The goal of the federal government's BRAIN Initiative is to accelerate the development and application of innovative technologies to produce a revolutionary new dynamic picture of the brain. Engel will build mathematical models of decision-making activity in two different areas of the brain. Engel will work with Associate Professor Anne Churchland on this project.

C. dos Santos

Assistant Professor Camila dos Santos was awarded the Pershing Square Sohn Prize for Young Investigators in Cancer Research. This is the fifth year the Alliance has awarded the prize to promising early-career, New York City–area scientists—this year, to six others in addition to Dr. dos Santos. She aims to find ways to prevent breast cancer by examining the epigenome, a system of molecular marks that change the way genes are expressed without changing the DNA itself. Her research builds on a correlation that has been observed for nearly 100 years: that a full-term pregnancy early in a woman's life dramatically reduces

her risk of developing breast cancer later in life. By analyzing the epigenome in animal models of breast cancer, Dr. dos Santos's group has already established that pregnancy changes the epigenome of breast cells known as mammary epithelial cells.

CSHL Fellow Lingbo Zhang aims to extinguish myelodysplastic syndromes (MDSs) and was recognized by the Edward P. Evans Foundation with an EvansMDS Young Investigator Award. This highly competitive award supports Zhang's translational research on MDS. Zhang is one of the first researchers to receive this award, created to support the development of the next generation of research leaders who will blaze a path toward cures for MDSs.

L. Zhang

To assess a potential therapeutic compound that Zhang identified and move the project toward clinical trials for MDSs, he is currently collaborating with a medicinal chemist at Northwell Health, with which CSHL formed a strategic affiliation in 2015. Using CRISPR gene editing to rapidly and precisely make changes to the genome, Zhang has screened MDS cells for a list of vulnerabilities, which he has since narrowed down to those that could be most effectively targeted with drugs.

CSHL Fellow Semir Beyaz received three different honors for his research, which looks at how dietary choices impact the body's immunity against cancer. Beyaz first received the Jeffrey Modell Prize, given by the Jeffrey Modell Foundation and the Harvard Committee of Immunology to a Harvard graduate student for excellence in his or her graduate career and dissertation.

S. Beyaz

He also received the Turkish American Scientists & Scholars Association (TASSA) Aziz Sancar Award, given to young Turkish researchers and scholars in STEM fields.

Additionally, Beyaz received the Sabri Ulker Early-Career Award from the Organizing Committee of Cell Symposia: Translational Immunometabolism for an abstract submission.

New Hires/Promotions

2018 brought a new CSHL Fellow, Semir Beyaz, and Assistant Professor, Tobias Janowitz, to pursue new, whole-organism approaches to cancer, obesity, and nutrition. Central to their efforts will be the historic 1953 Demerec Laboratory, under renovation and scheduled to open in 2019. Alexander Dobin, who had been a postdoc at CSHL since 2008, also joined as Assistant Professor to further investigate cancer genomics.

Plant biologist Professor Zach Lippman began his CSHL career as a Ph.D. student; he returned to join the faculty after a postdoc in Israel. This year he was named a Howard Hughes Medical Institute (HHMI) Investigator. CSHL is proud of this addition to our existing HHMI Investigators, Professors Rob Martienssen and Leemor Joshua-Tor.

Molly Hammell and Dan Levy were promoted to Associate Professor.

S. Beyaz

T. Janowitz

A. Dobin

Z. Lippman

Education Highlights

Meetings & Courses Program

CSHL Meetings this year attracted 7,000 participants from more than 50 countries to the main campus. The 83rd Cold Spring Harbor Symposium, Brains and Behavior: Order and Disorder in the Nervous System, explored how fundamental brain research and technologies are translating to improved brain health and treatments for psychiatric and neurological disorders. The symposium was supported by the Tianqiao & Chrissy Chen Institute. Single Biomolecules and Nutrient Signaling were new additions to the meetings program. The Evolving Concept of Mitochondria: From Symbiotic Origins to Therapeutic Opportunities was the topic of the 10th meeting of the Genentech Center, History of Molecular Biology & Biotechnology series.

The Cold Spring Harbor Asia (CSHA) conference program drew 3,500 scientists to symposia, meetings, and Banbury-style discussions designed for scientists from the Asia/Pacific region. CSHL was pleased to sign a new partnership agreement with Suzhou Industrial Park to both extend and expand the commitment to operating meetings and courses on the Dushu Lake campus for another decade.

Covering a diverse array of topics in molecular biology, neurobiology, structural studies, and bioinformatics, 700 instructors, lecturers and assistants have come to teach at CSHL from universities, medical schools, research institutes, and companies around the world. In 2018, 650 trainees—advanced graduate students, postdocs, and faculty—attended courses lasting from one to three weeks. The latest addition to the program is the course on Cryoelectron Microscopy.

The Courses program relies on grants and foundation support, including major support from the Helmsley Charitable Trust, the Howard Hughes Medical Institute, the National Institutes of Health, and the National Science Foundation. 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.

Banbury Center

This year's 18 meetings demonstrated two of Banbury's core strengths: bridging interdisciplinary divides and hosting discussions at the frontiers of science and technology. Discussions covered the legal and ethical implications for the growing neuromonitoring and neuromodulatory devices

Banbury Conference Center meeting

market, expected to top $3 billion by 2020; explored the use of DNA to store data; considered comprehensive and community approaches to HIV prevention; considered new questions about aging from the long-living bat; and took aim at the opioid epidemic from a practical, policy standpoint.

The Evolving Phenomenon of Direct-to-Consumer Neuroscience meeting produced a January 2019 publication in *Science* suggesting ways to provide systematic support for regulatory agencies, funding bodies, and a public that is thirsty for knowledge about the efficacy of consumer-targeted neurotechnology products.

A second paper resulting from the 2016 Banbury Meeting Diagnostic Tests for Lyme Disease: a Reassessment and Pathways Forward was published in *Clinical Infectious Diseases*, marking a major advance in the ability to diagnose and treat Lyme disease sooner.

Signals of Trust in Science Communication gathered a diverse group of eminent scientists, journal editors, science writers, and communications experts to debate complex issues surrounding trustworthiness in science. A Twitter campaign associated with the meeting allowed users from across the world to share their perspectives on the issue.

Sponsored by CSHL, Increasing Gender Diversity in Biosciences convened to identify practical solutions to better recruit, promote, and support women in science. A report from the meeting has been accepted for publication in the prestigious journal *Science* in 2019.

Banbury continues to attract financial support from across sectors, with almost half drawn from not-for-profit organizations.

Watson School of Biological Sciences

CSHL welcomed its 20th incoming class of Ph.D. students from the United States, Canada, China, France, Hong Kong, India, Pakistan, and Turkey. A goal of the program is to graduate students faster than students in comparable Ph.D.-granting institutions and position them to secure excellent jobs early in their careers. As of this year, 105 CSHL Ph.D. graduates are now thriving in the world.

Twenty-seven graduates have secured tenure-track faculty positions and are receiving federal grants and publishing papers as independent researchers. One alumnus, Dr. Zachary Lippman, is a professor at CSHL and this year became the first CSHL graduate to be named a Howard Hughes Medical Institute Investigator. The School's alumni have also moved into influential positions in administration, publishing, consulting, and industry—with one of this year's graduates taking a data scientist position. During the year, scientific papers published by students appeared in major journals, bringing the cumulative total to 400.

WSBS entering Class of 2018

At the 2018 graduation ceremony, five students were awarded Ph.D. degrees. Drs. David and Leon Botstein were awarded honorary degrees. David Botstein is a prominent geneticist, CSHL course instructor, and CSHL Trustee from 2003 to 2013. Leon Botstein was the youngest person appointed as college president in American history and currently is the President of Bard College and the music director of the American Symphony Orchestra.

From June through August, 20 undergraduates from around the world performed advanced research in the laboratory of a CSHL faculty member. In its 59th year, the annual immersive experience called the Undergraduate Research Program reaped intellectual as well as social rewards for the participants. The equally innovative Partners for the Future program brought gifted local high school students to CSHL labs for hands-on research experience.

DNA Learning Center

Just as a universal product code (UPC "barcode") uses a unique set of bars to identify each consumer product, a DNA barcode is a unique set of DNA "letters" that identifies each living thing.

Students and faculty swabbing snakes to collect microbiomes

Over the last eight years, the DNALC has developed simplified biochemistry and bioinformatics analysis that puts DNA barcode research within reach of students and citizen scientists. Funding from the Thompson Family Foundation, the Laurie Landeau Foundation, the Simons Foundation and the Pinkerton Foundation supported barcode projects by 582 students from 80 high schools across New York City and Long Island this year.

The DNALC's barcoding infrastructure also supports course-based *undergraduate* research experiences (CUREs), which have been shown to increase graduation rates and student retention in STEM disciplines. In October, DNALC began a new 5-year project with funding from the National Science Foundation (NSF) program Improving Undergraduate STEM Education (IUSE). In addition to popularizing our existing barcoding platform for student projects, the initiative will develop affordable technology for metabarcoding—which uses next-generation sequencing to identify the variety of microbes, fish, or other living things in an environmental sample. The project will train and mentor 80 college faculty as they implement CUREs in a variety of classes and school settings. Among key collaborators on the project are City Tech, where we will open a new DNALC in 2020, and James Madison University (JMU), whose barcoding CURE serves 500 students per semester.

During the academic year, 21,176 students conducted labs at Dolan DNA Learning Center, DNALC West and Harlem DNA Lab; and 1,347 students attended week-long summer camps. An additional 7,905 students conducted in-school labs led by DNALC staff, and 1,983 used footlocker kits. Also, this year, 5.6 million visitors accessed DNALC's suite of multimedia resources online, including 4 million visits to DNALC websites, 911,378 views of YouTube videos, and 661,726 downloads of smartphone/tablet apps, the *3D Brain*, *Weed to Wonder*, and *Gene Screen*.

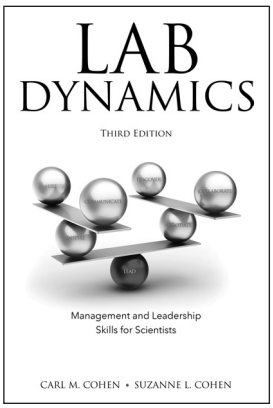
The DNALC has been a partner of the Breakthrough Prize competition, delivering a state-of-the-art science laboratory to the high school of the Junior Breakthrough Challenge winner. In 2016, Hillary Diane Andales entered the Junior Breakthrough Challenge, which asks high school students to make a video about their favorite concept in science or math. Among the thousands of submissions from all over the world, Hillary's video was voted the most popular, with a whopping 40,000 Facebook "likes."

Although the video did not win the competition's grand prize, it did earn Hillary's Philippine Science High School a new $100,000 laboratory classroom designed and equipped by the DNALC. In 2018 she submitted another video and won a $250,000 scholarship and *another* $100,000 DNALC-designed laboratory for her school.

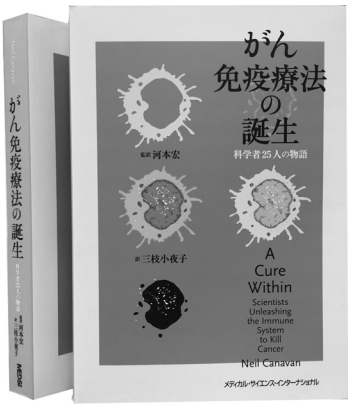
Cold Spring Harbor Laboratory Press

The Cold Spring Harbor Laboratory Press provides scientists worldwide with authoritative, affordable, and up-to-date information to further their research and aid in their career development. The CSHL Press continues to respond creatively and pragmatically to the opportunities offered by both online and print distribution and to the changing landscape of funding and business models in the sharing of scientific information.

The seven established research and review subscription journals continued to publish highly valued content and maintain or expand their international audience. *Genes & Development* and *Genome Research* remained at the top of their disciplines among primary research journals. *CSH Molecular Case Studies* (*MCS*), a newer open access title, is gaining ground among authors who have obtained results from the application of precision medicine techniques to one patient or a small cohort. Launched in April 2018, *Life Science Alliance* (*LSA*) is a new open access journal owned and published jointly by the Laboratory, the European Molecular Biology Organization (EMBO), and Rockefeller University. Using a unique cross-publisher "cascade" publishing model, *LSA* is a publication channel for manuscripts referred by nine



Lab Dynamics, 3E



A Cure Within, Japanese translation

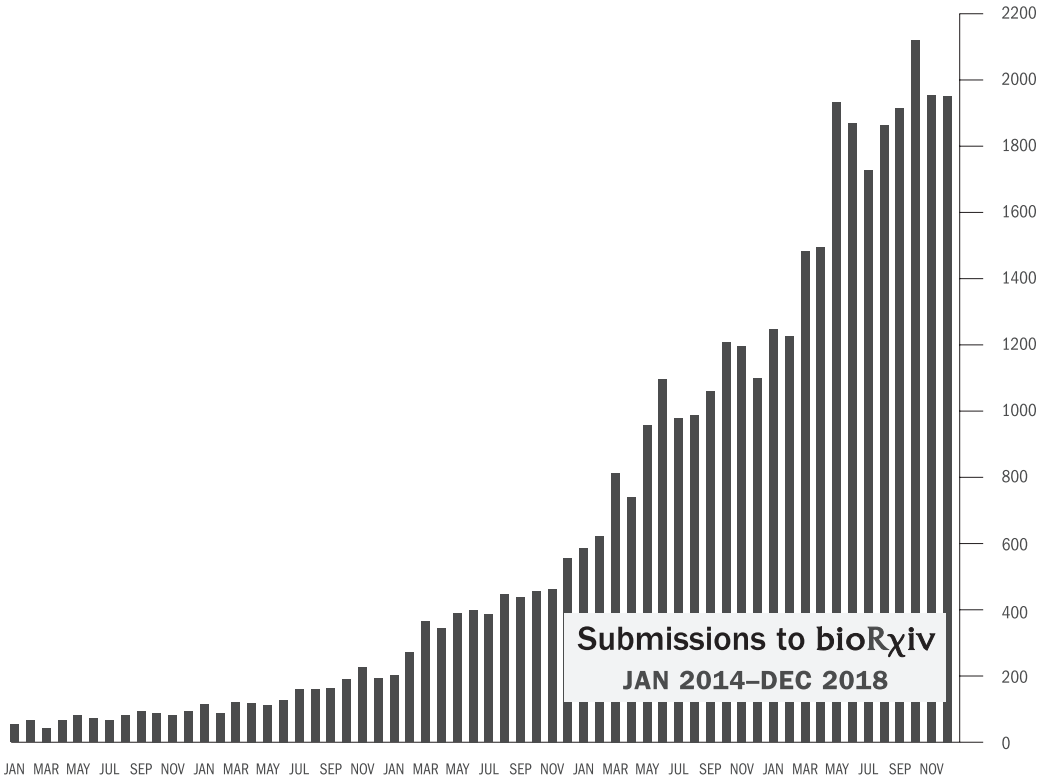
of the highly selective journals published by the three partner organizations.

The CSHL Press published 15 new book titles in 2018. Ten were themed collections of articles published in the *Perspectives in Biology* and *Perspectives in Medicine* journals. This publishing model, a successful marriage of serial online and print book publishing, successfully engages thought leaders as editors and distinguished investigators as authors. The handbook *Lab Dynamics* was published in a third edition that for the first time assists principal investigators in the challenging responsibilities of interviewing prospective team candidates and assessing performance.

Published in 2017, *A Cure Within: Scientists Unleashing the Immune System to Kill Cancer* by Neil Canavan continued to be a best seller, with a Japanese translation complete and a Chinese translation in progress—and gained added impetus with the award of the 2018 Nobel Prize in Physiology or Medicine to two scientists featured in the book, James Allison and Tasuko Honjo.

bioRxiv, the Preprint Server for Biology

A preprint is a research manuscript distributed by its authors before certification by peer review and publication by a journal. The Laboratory's preprint server, bioRxiv, turned five in 2018 and, with major support from the Chan Zuckerberg Initiative (CZI), continued its rapid



Growth in bioRxiv submissions

growth, doubling in size with 20,000 new submissions from more than 100 countries. Each month, papers on the server are read more than 4.5 million times and discussed in social networks and dedicated preprint assessment sites. The server is clearly accelerating science: 70% of bioRxiv manuscripts are shared for community evaluation as long as two years (median six months) before journal publication. Thirty journals now enable authors to simultaneously submit a manuscript and post it on bioRxiv, and 130 journals will accept automatic submission of preprints for editorial consideration. In 2018, an additional CZI grant made possible the conversion of all bioRxiv papers into XML format so they can be read in a web browser without downloading. bioRxiv continues to transform the way biologists communicate their science.

Marilyn Simons, Bruce Stillman, and Jamie C. Nicholls

Board of Trustees

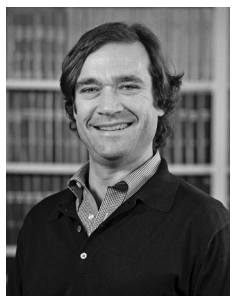
Dr. Marilyn Simons, president and co-founder of the Simons Foundation with her husband Dr. Jim Simons, CSHL honorary trustee, was elected chairman of the CSHL Board of Trustees in November. Marilyn was previously the vice-chairman of the Board, and led the successful 125th Anniversary Capital Campaign. She takes the baton from Jamie C. Nicholls, who served as chairman from 2010 to 2018. In recognition of Nicholls' unprecedented efforts to ensure the institution's financial strength and stability, as evidenced by the doubling of the endowment to more than $640 million during her tenure, Jamie was named the Laboratory's first-ever lifetime trustee.

New trustees elected in 2018 include Bruce Ratner, chairman of Forest City, New York; Dr. Stuart Weisbrod, former CSHL postdoctoral fellow and current chief investment officer of Iguana Healthcare Partners; Dr. Karel Svoboda, former CSHL professor and current Howard Hughes Medical Institute (HHMI) investigator and group leader at HHMI Janelia Research Campus; Dr. Elaine Fuchs, HHMI investigator and professor at the Rockefeller University; and Geoffrey Robertson, director of Business Assistance at the Vermont Sustainable Jobs Fund—who is the grandson of Charles and Marie Robertson, who in 1973 generously provided the initial gift to seed the CSHL endowment.

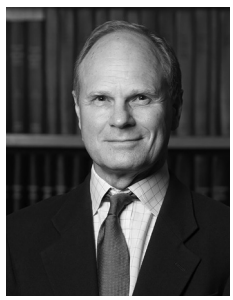
John P. Tuke was appointed chief operating officer in November 2018. He had been the chief financial officer of the Hotchkiss School for more than 19 years, overseeing a broad range of financial, operational, risk management, and strategic activities.

K. Svoboda

E. Fuchs

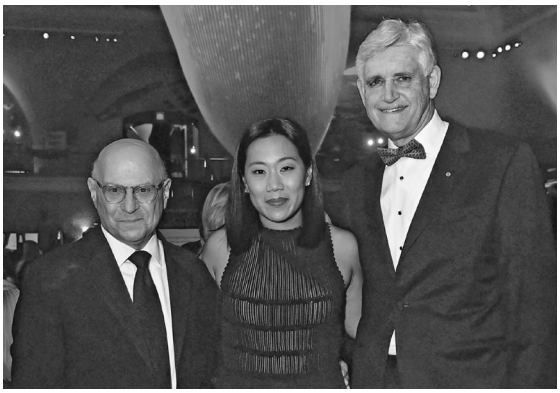


G. Robertson



J. Tuke

W.D. Ayres

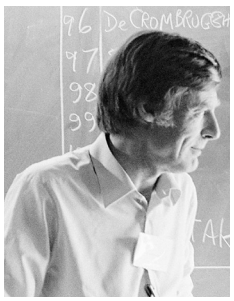


Larry Norton, Priscilla Chan, and Bruce Stillman

John succeeded W. Dillaway Ayres, who helped lead this organization with distinction for 20 years, setting the highest of standards—but, more importantly, was a leader in maintaining the collegial and entrepreneurial culture that is integral to the Lab's success.

The power of the CSHL Board of Trustees was demonstrated at the institution's record-breaking Double Helix Medals Dinner, which raised $4 million honoring Mark Zuckerberg and Dr. Priscilla Chan of the Chan Zuckerberg Initiative and renowned oncologist Dr. Larry Norton. Through other events and fund-raising initiatives, trustees and friends of CSHL rallied to raise a total of >$7 million of unrestricted money that supports the Lab's most innovative research initiatives. The Helix Society, a planned-giving initiative, continues to grow in members and dollars, becoming a vital source to guarantee the Lab's future.

CSHL Director John Cairns



J. Cairns

The Laboratory fondly remembers John Cairns, CSHL Director from 1963 to 1968, who passed away in late 2018. Cairns is known for pioneering work in DNA autoradiography. A physician and molecular biologist trained at Oxford, Cairns saw the Laboratory as "Arcadia," an unspoiled, harmonious wilderness, a mythical place with scientific ideal. He was dedicated to the Lab's survival during stressful financial times in the 1960s. See the special tribute to him in this publication.

Business Development & Technology Transfer

A. Whiteley

In April, CSHL announced the appointment of Andrew Whiteley as the new vice president of Business Development and Technology Transfer. He had served as executive in residence at CSHL since November 2015. Andrew succeeds Teri Willey, who served in this position since 2013.

This "innovation" team are business agents for CSHL and its scientists, helping to bring discoveries made at the Lab to the public through intellectual property licensing, industry collaborative research and new ventures. Highlights of 2018 included:

- Monetizing the assets from the development of the 2016 FDA-approved spinal muscular atrophy drug Spinraza®, which added $82 million to the endowment and contributed royalty streams that added $8 million to the Science Fund for reinvestment into research here.
- More than $3.58 million in licensing revenue and $630 million in sponsored research funding was received under agreements negotiated and managed by this team.

Library and Archives

The Message

All educational and scholarly programs are now part of the Center for Humanities Studies of Molecular Biology, an interdisciplinary destination for historians, scholars, researchers, and artists to take advantage of the rich history found in the original materials in our archives for their humanities projects. The Center is also home to all Library and Archives–hosted events related to modern biology.

In August, the Center hosted *New York Times* columnist and science writer Carl Zimmer, who spoke about his new book, *She Has Her Mother's Laugh*. In October, the Center hosted a play about a major event in modern science history. The new play, *The Message*, written by Keith Burridge, directed by Hal Brooks, and starring Broadway actors Brad Cover, Dominic Cuskern, and Rachel Botchan, was based on the discovery of messenger RNA (and written after Burridge's extensive research in our collections).

The Center has hosted two international meetings: a workshop on Historical Research on Model Organisms in Biology, and the annual History of Science meeting The Evolving Concept of Mitochondria. The meeting on mitochondria was attended by more than 150 scientists. Videos of the speakers' talks, along with their presentation slides and more, are available on the meeting website at http://library.cshl.edu/Meetings/Mitochondria. The workshop on model organisms gathered 21 scientists and historians from around the world to discuss the historical rise of select species from the wide array of experimental organisms to the vaunted status of model organisms and to formulate a suggested path forward for historical study of this aspect of the history of biology.

Sydney Brenner Research Scholarship recipient Matthew Cobb presented a talk on his research from the Archives about the working relationship between two Nobel laureates, Francis Crick and Sydney Brenner.

Based on an idea from Jim Watson to create a book about the major players of the Human Genome Project (HGP), editors Mila Pollock, Jan Witkowski, and Dick McCombie published *Faces of the Genome*. It consists of pencil sketch portraits of scientists involved in the HGP by famed Australian artist Lewis Miller. The original sketches are housed in the Archives. The book also contains biographical sketches of the scientists, written by their colleagues, and an introduction by Watson.

Infrastructure

Made possible with funds raised by the 125th Anniversary Capital Campaign, reconstruction of the Demerec Laboratory took place during the entire year, with scheduled completion in 2019. This major construction project brought a unique set of challenges, including the need to create a modern laboratory building within a historically sensitive building. The project's location at the center of campus near the main entrance added additional considerations to ensure unimpeded normal campus operations, including a busy Meetings & Courses Program year.

The long-overdue renovation of Dolan Hall was completed and fully operational for the second half of 2018. Guest rooms were renovated and improved to meet modern expectations, resulting in a modern boutique-style property with high-quality—albeit small—guest rooms.

The Laboratory also undertook a number of infrastructure renewal projects, including:

- *North Chiller Plant: chiller replacement.* Two aging chillers supplying the Hillside Laboratories were replaced with a larger, more energy-efficient chiller. This new high-efficiency unit offers a far greater service life and operates at a far lower cost than the preexisting chillers.

- *South Chiller Plant: emergency generator replacement.* The diesel emergency generator serving the Marks, James, and Freeman Laboratories suffered a catastrophic failure, requiring emergency replacement.
- *James Laboratory: walkway replacement.* The elevated walkway entrance to the James Laboratory had degraded over time, becoming unsafe for use. This walkway was reconstructed to current standards.
- *Tiffany House: retaining wall.* The Laboratory had been managing drainage and water issues with the Tiffany House for a number of years. A major project was undertaken to construct a new retaining wall behind the house and to create sufficient drainage to protect the property.
- *Housing Improvements.* The Laboratory continued its program of modernizing and improving its housing stock, with a number of renovations in the Robertson, Davenport, and Moore's Hill Road properties.

The Laboratory continued its ongoing program of researching and implementing energy conservation projects. These include both equipment and lighting retrofits with the intention of providing improved lighting and comfort at a lower cost and a reduced carbon footprint.

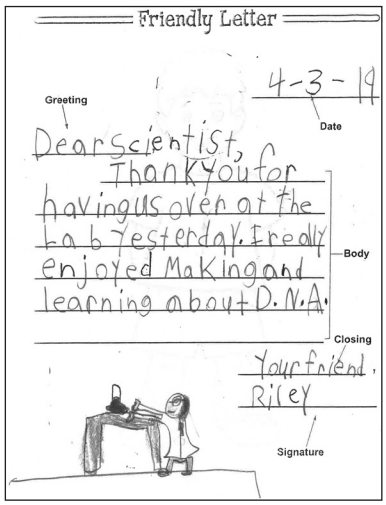
Community Outreach

The Public Affairs Department works closely with faculty, students, and employees across the Lab to create opportunities for the public to engage with the institution. This includes public tours, lectures, and talks, concerts, and various channels of regular communication through digital and printed materials available at cshl.edu. The Lab's digital platform was upgraded in 2018, making information about CSHL more easily accessible to audiences across the globe. An example of the department's success in digital content creation and distribution is *Base Pairs*, the three-season podcast series about the power of genetic information, which was selected as a finalist in the 2018 Webby Awards.

Base Pairs with Brian Stallard and Andrea Alfano

The Lab's public tour program attracted nearly 1,400 visitors to the Bungtown Road campus from spring through fall. Fifty-four group tours and 19 weekend public tours were guided by our guide team of 15 Ph.D. students.

CSHL remains active in our local schools, as faculty, students, and employees volunteer time to share our science and personal career stories with students and their families. In addition to the varied volunteer opportunities, the Lab annually hosts the Cold Spring Harbor School District's first graders and their parents for a hands-on science fair. This year's experimental stations shared knowledge ranging from brain biology to states of matter to DNA codes and chromatography. All of these activities are developed and delivered by Watson School graduate students and DNA Learning Center teachers.


Friendly Letter

4-3-19

Greeting

Date

Dear Scientist,

Thank You for having us over at the lab yesterday. I really enjoyed Making and learning about D.N.A.

Body

Closing

Your friend,

Riley

Signature

Thanks for the science fair

In addition to a series of scientific lectures that invites the community to the Lab's Grace Auditorium, a more casual event called Cocktails & Chromosomes is gaining a significant local following. With neighborhood bars as the

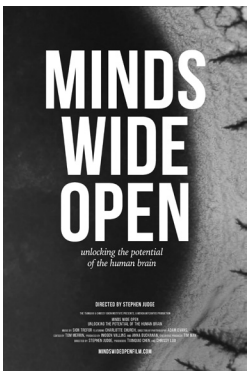
venue, this series of talks is strictly for nonscientists. CSHL faculty presenters make a special effort to avoid scientific jargon and simply share their curiosity about the wonder of their science with our neighbors.

CSHL Public Presentations

February 11: Screening and discussion at Cinema Arts Centre in Huntington Co.; *Food Evolution*. Panelists: **David Jackson, Ph.D.,** professor, CSHL; **Zachary Lippman, Ph.D.,** professor, CSHL; **Ullas Pedmale, Ph.D.**, assistant professor, CSHL; **Doreen Ware, Ph.D.**, molecular biologist, USDA ARS, adjunct associate professor, CSHL; co-presented by Cold Spring Harbor Laboratory & Science Advocacy of Long Island.

April 23: Public lecture, Energy from Thin Air: Basic Research to Biofuels. **Rob Martienssen, Ph.D.**, professor, CSHL; **Frank O'Keefe**, founder & CEO, Infinitree.

May 29: East coast film premiere of Tianqiao & Chrissy Chen Institute's (TCCI) documentary, followed by Q&A; *Minds Wide Open: Unlocking the Potential of the Human Brain*. TCCI was the exclusive supporting partner of the 2018 Cold Spring Harbor Symposium.



Minds Wide Open

June 12: Public lecture, Metastasis & Immunity: How Immune Cells Can Help Cancer Spread or Stop It in Its Tracks; co-sponsored by CSHL, US Trust, Northwell Health, and St. Johnland Nursing Center. **Mikala Egeblad, Ph.D.**, associate professor, CSHL; **Sylvia Adams, M.D.,** associate professor, Department of Medicine, director of Clinical Research, Breast Cancer Disease Management Group, NYU Medical Center.

June 20: *Cocktails & Chromosomes* at Six Harbors Brewing Co. **Jessica Tollkuhn, Ph.D.**, assistant professor, Cold Spring Harbor Laboratory.

July 31: Screening and discussion at Cinema Arts Centre in Huntington Co.; *The Most Unknown*. Panelists: **Bruce Stillman, Ph.D.,** professor, president & CEO, CSHL; **Scott McLennan, Ph.D.,** professor, Stony Brook University; **Lisa Miller, Ph.D.**, biophysical chemist, Brookhaven National Laboratory; co-presented by Cold Spring Harbor Laboratory & Cinema Arts Centre as a Science on Screen event.

October 5: Play by **Keith Burridge**. *The Message: A Play about the Discovery of Messenger RNA*. Panel including **Wally Gilbert, Ph.D.**; **Matthew Meselson, Ph.D.**; **James D. Watson, Ph.D.**

October 23: Public lecture, Genetic Privacy: Friend or Foe? 2018 Lorraine Grace lectureship on societal issues of biomedical research. **Yaniv Erlich, Ph.D.,** chief science officer, MyHeritage, associate professor of Computer Science, Columbia University [leave of absence], adjunct core member, New York Genome Center.

Cocktails & Chromosomes

December 5: *Cocktails & Chromosomes* at Six Harbors Brewing Co. **Tatiana Engel, Ph.D.**, assistant professor, Cold Spring Harbor Laboratory.

CSHL Public Concerts

April 20: Tomer Gewirtzman, piano
May 4: Yoonah Kim, clarinet
May 18: Naomi Louisa O'Connell, mezzo soprano

Naomi Louisa O'Connell

Employees celebrating Top Long Island Workplaces win

September 14: Argus Quartet, string quartet
September 28: Dominic Cheli, piano
October 12: SooBeen Lee, violin

Looking Forward

CSHL received a special honor this year from our own employees, winning Top Long Island Workplaces 2018. *Newsday* surveyed employees across Long Island on the quality of their workplaces. The anonymous employee surveys were analyzed by a third party. As part of the large company category (more than 500 employees), CSHL shared the honor with only 14 other institutions. Thank you to all who contribute to the success of this institution and the productive environment of all of our campuses. With your support, the future is bright.

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