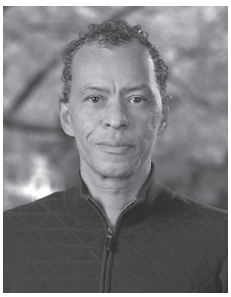
Highlights of the Year

Research

In 2021, hundreds of scientists working in nearly 60 Cold Spring Harbor Laboratory (CSHL) research groups published their findings in the world's major research journals. Their efforts reflect the full spectrum of CSHL's programs in Cancer, Neuroscience, Plant Biology, Quantitative Biology, Genomics, and a new chemistry lab. The following is a sampling of this year's important findings.

Pinpointing Cancer's Origins



L. Trotman

CSHL Adjunct Professor Pavel Osten and Professor Lloyd Trotman have pioneered a new method to track how prostate cancer progresses in mice, from its birth to its spread into other tissues. The pair combined their expertise in whole-organ imaging and prostate cancer to track how a single cancer cell can grow into a tumor and spread to other organs. For the first time, researchers can study a tumor as it grows in a setting that accurately mimics the disease in real life. The study was led by Julian Taranda, a former postdoc in the Osten laboratory, and was published in *Cell Reports*.

The researchers used a virus to transform as little as one normal mouse prostate cell into a cancerous cell. This lone cancer cell was located using a microscope technique called whole-organ serial two-photon tomography. The tomography machine is fully automated. It takes an image of all the cells on the top layer of an organ, slices off that piece, images what is in the next layer, and repeats the process until it has photographed the entire organ. Then, using artificial intelligence, a computer creates a 3D reconstruction of the organ at single-cell resolution. The scientists hope this versatile new method will help tackle unexplored questions about the early steps of cancer's growth and escape into other organs, wherever it starts.

Cushy Homes for Cancer

M. Egeblad

Cancer cells live in a complex neighborhood populated by immune cells, blood vessels, and other structures. Cells signal each other as to who they are and what they want. Cancer cells may hide their identity so they can grow and spread more easily. CSHL Professor Mikala Egeblad wants to know what creates an ideal microenvironment for a wandering cancer cell. She reasons that if she can decode the signals in the neighborhood, she may find ways to harness those signals to defeat cancers.

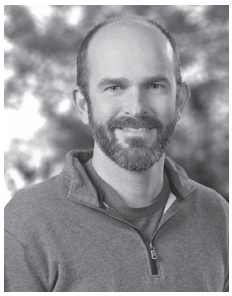
Breast and ovarian cancer cells can reprogram immune cells to make them into "tumor-associated macrophages" (TAMs), which act like a security team hired by the cancer cells to protect themselves. Egeblad's laboratory found that interferon-gamma plus an immune system activator re-reprogrammed breast cancer TAMs so they would attack the cancer. The two drugs were also extremely effective against ovarian cancer in mice. In both cancers, the treatment slowed metastases and made ovarian tumors more susceptible to chemotherapy.

Lessons learned about the cancer microenvironment can be applied to COVID-19. Neutrophils, a type of immune cell, can form sticky neutrophil extracellular traps, or NETs, which normally trap pathogens. However, too many NETs can be toxic—especially in the lungs, where they can damage tissue and cause respiratory distress. Thus neutrophils, like macrophages, could become therapeutic targets.

Cancer's Sweet Tooth

CSHL Professor Christopher Vakoc and his laboratory discovered that acute myeloid leukemia (AML) cells depend on a single transporter to get the essential sugar inositol into the cell. Cancers

streamline certain cell processes, "putting all their eggs in one basket" with a single pathway. Vakoc can then develop treatments to knock out that remaining pathway and kill the cancer cells.



C. Vakoc

Most cells either get inositol from the bloodstream (it is present in many foods) or make it themselves. Because there is plenty of sugar available outside the cell, some cancer cells decided to rely on the inositol transporter to capture it and stop making it inside the cell. If researchers can find a treatment that can turn off or block this transporter, the cancer cells would starve. This method would leave normal cells unharmed because they can make inositol on their own. Vakoc reported his findings in *Cancer Discovery*.

Vakoc says his work suggests a few roads to developing a therapeutic: "You could make an antibody that just sticks to this transporter. It doesn't need to get into the cell, and it could shut off the transport function. The other possibility, from a drug development point of view, is inositol. You could build a molecular medicine that sort of looks like inositol, but has a few chemical differences that can clog the transport function."

Predicting Cancer's Path

Assistant Professor David McCandlish and collaborators used the statistical method of density estimation in a new way: to predict how combinations of genetic mutations cause different types of tumors. McCandlish says, "This is what's fascinating about mathematical research. Sometimes you see connections between topics that seem so different, but at a mathematical level, they use the same ideas."

D. McCandlish

McCandlish mapped the combinations of mutations most likely to occur in a particular protein and in the same cancer cell. It is straightforward to predict the co-occurrence of a couple of events, like how often you might find two people of the same height in a group. But for complex biological sequences, such as the hundreds of amino acids that make up a protein, predicting the probability of each potential sequence becomes astonishingly complex. "Sometimes, with one mutation in a protein sequence, the protein works fine," explains McCandlish. "And with a second mutation, it still works fine, but then if you put the two of them together, you get a broken protein. We've been trying to come up with methods to model interactions between any number of mutations." Their new method can predict how hundreds of thousands of different mutation combinations impact the function of a protein.

The team published the study in the *Proceedings of the National Academy of Sciences* and made their density estimation software available publicly.

Estrogen Gives Mice the Moves

Female animals are most active when estrogen levels are high, increasing their chances of encountering a mate when pregnancy is most likely. Mice with low levels of estrogen are more sedentary than ones with high levels. Women also become more sedentary as estrogen levels decrease during menopause. CSHL Assistant Professor Jessica Tollkuhn and her collaborators at the University of California, San Francisco, have now traced this hormone-driven activity to a cluster of estrogen-sensitive cells in the brain.

J. Tollkuhn

Tollkuhn and her team study the profound impact estrogen has on the brain, where it not only influences activity levels, but also modulates mood, alters sleep patterns, and helps control body temperature. In the brain, the hormone latches onto an estrogen receptor (ERα), changing the activities of specific genes. Tollkuhn and colleagues have found nearly 2,000 sites within the genome that interact with ERα, suggesting the hormone regulates hundreds of different genes in the brain.

One of those genes is *Mc4r*. The team's experiments in mice revealed how the hormone provokes signaling changes inside estrogen-sensitive neurons. Importantly, they found they can mimic these effects without increasing estrogen exposure, simply by activating *Mc4r* in the relevant neurons.

The team's findings suggest it may be possible to develop targeted therapies that restore specific benefits of estrogen signaling—without the side effects of hormone replacement.

Every Brain Cell Counts

P. Osten

CSHL Adjunct Professor Pavel Osten and his laboratory mapped cells and connections within the mouse primary motor cortex. They categorized different cell types throughout the brain in a quantitative brain-wide (qBrain) catalog. With this method, the researchers can standardize a 3D map of the 100 million neurons in the mouse brain and, in the near future, even the 100 billion neurons in the human brain.

Osten's technique starts with labeling brain cells of interest to identify classes of cells or particular pathways. The brain is then preserved and imaged automatically at high resolution. Each brain is analyzed by a computer that can count the cells or trace the pathways, comparing it to previously mapped brains. The entire process, automated after the brain is preserved, takes 12 to 32 hours per mouse. The researchers then compare new brains to their standardized 3D maps to figure out gender differences within a species, development stages, and diseases. They already discovered anatomical differences between male and female mouse brains associated with behavioral differences.

Osten and his laboratory were a part of the founding group of scientists for the NIH-funded Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative–Cell Census Network (BICCN). Similar in scope to the Human Genome Project, BRAIN is providing a foundation for studying the mammalian brain with new methods.

Helpless No More

L. Van Aelst

Everyone faces stress occasionally, whether in school, at work, or during a global pandemic. CSHL Professor Linda Van Aelst studies how individuals respond to stress. Her laboratory studied the mouse gene *Ophn1*, which plays a critical role in developing brain cell connections, memories, and stress tolerance. When *Ophn1* is removed in a specific part of the brain, mice express depression-like helpless behaviors. The researchers found three agents, including a drug called fasudil, that could reverse this effect.

To test for stress responses, the researchers put mice into a two-room cage with a door in between. The floor in one room provides a light shock to their feet, and normal mice leave that room. But animals lacking *Ophn1* sit helplessly in that room without trying to escape.

Van Aelst's laboratory deleted the *Ophn1* gene in different brain regions. Removing *Ophn1* from a circuit in the prefrontal cortex known to influence behavioral responses and emotion induced the helpless phenotype. Overactivity in a particular part of the circuit was the key.

In humans, mutations in the *Ophn1* gene cause a rare X-linked disease that includes poor stress tolerance. Van Aelst hopes that understanding the complex circuit behind *Ophn1*-related stress responses will lead to better treatments for humans. The team published their results in *Neuron*.

Robots Explain Their Thoughts

Brain-like artificial networks are often referred to as a "black box" because researchers do not know how they learn and make predictions. CSHL Assistant Professor Peter Koo and his team reported new ways to peek inside the box and identify key features on which the computer program relies, particularly when trying to analyze complex RNA and DNA sequences.

P. Koo

Residual Bind is a type of AI program called a deep neural network. It predicts the ability of RNA sequences to bind to proteins. Koo and his team developed a new method, called global importance analysis, that "quizzes" this AI program to figure out what rules it learned on its own and whether they are the right ones. They discovered that the network considered more than just the spelling of a short stretch of RNA. It factored in how the RNA strand might fold over and bind to itself, how close one RNA pattern is to another, and other features.

Koo's team also reported a new way to train a type of AI network, called a convolutional neural network, to predict the function of DNA sequences. This new method allows machine learning researchers to identify some key features that lead to the computer's decision-making process.

Koo and his colleagues published their findings in *Nature Machine Intelligence* and *PLOS Computational Biology*.

Shady Communications

Shade avoidance is a vital survival strategy for plants, but it's a problem for farmers, says CSHL Assistant Professor Ullas Pedmale. When a plant finds itself in the shade, it directs its resources to reach for the light. This shade response limits the density of crop plantings and thus limits yields. Pedmale and his laboratory discovered a group of proteins called WRKYs that are responsible for stunting root growth in the shade.

U. Pedmale

Pedmale's team compared the roots of tomato and *Arabidopsis thaliana* seedlings grown in light to the shorter, less developed roots of plants grown in shade. Postdoc Daniele Rosado and colleagues found hundreds of genes that plants use to respond to stress were switched on in the shade-grown plants—including dozens that encode WRKYs.

To confirm that WRKYs limit root growth, Pedmale's team engineered plants in which specific WRKY genes were highly active in light and shade. They found that plants with high levels of certain WRKY proteins grew the same stunted roots seen in shade-grown plants, even when provided with plenty of light. The plant's stems, in contrast, grew at a normal rate.

Pedmale hopes this work will help researchers develop plants that can thrive under more crowded conditions, withstand extreme weather, and pull carbon dioxide out of the air into extensive root systems. The research was published in *Plant Physiology*.

Corn Evolution

Doreen Ware, a CSHL adjunct professor and research scientist at the U.S. Department of Agriculture, and her colleagues published the genome sequences of 26 different strains of corn in *Science*. They describe a large portion of the genetic diversity found in modern corn plants and reveal new genetic insights valuable for optimizing the crop for changing climates.

D. Ware

Like a continental landscape, genomic maps have areas that are full of features (like well-mapped cities), whereas others are more like deserts (vast and uncharted). With recent techniques, the team of scientists charted difficult stretches of the genome, even the deserts. These complete genomes allow researchers to locate and study both important crop genes and the nearby regions that regulate their use. Ware notes, "we had little access to the regulatory architecture of corn before."

The new collection reveals how the corn genome was shuffled over time. Ware says, "Different strains have experienced different environments. For example, some came from tropical environments, others experienced particular diseases, and all those selective pressures leave a footprint of that history."

Equipped with more detailed maps of the corn genome, scientists have a head start in developing crops for a rapidly changing climate. Ware explains, "The genomes provide broader insights into corn genetics, and this, in turn, can be used to start optimizing corn to grow in future environments."

Instant Polymers


J.E. Moses

A multi-institutional team of chemists, including CSHL Professor John E. Moses, Nobel laureate K. Barry Sharpless from Scripps Research, and Han Zuilhof of Wageningen University found a way to modify and use a dangerous gas called SOF_4 as building blocks for new products. In a paper in *Nature Chemistry*, they describe a new set of modifiable polymers made from SOF_4.

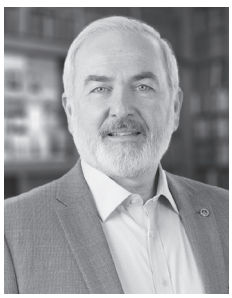
The team used a type of rapid and reliable chemistry known as click chemistry to "click" molecules together without producing toxic byproducts. The SOF_4 molecule acts as a hub to link together diverse components into a modular family of new—and potentially valuable—drugs and polymers.

The reactions are fast and produce very little waste or dirty by-products. Moses says, "That's why click chemistry is great. These polymers could be made in one day. As long as we have the gas, we could do all that chemistry in one day, make a polymer, and post-modify it in one day. That's incredibly fast."

This new chemistry will allow scientists to generate a vast new library of polymers, each with its own distinct properties and applications in drug discovery and material science. Moses says, "The opportunity for these polymers, I think, is infinite. There are so many things we can do with it. We're limited by our imagination."

Research Faculty

Awards


A. Krainer

Professor Adrian Krainer was awarded the 2021 Wolf Prize in Medicine for his contributions in biochemistry and molecular genetics and his fundamental mechanistic discoveries regarding RNA splicing. Awarded by the Wolf Foundation and the President of the State of Israel, the prize honors people for advancing science and art for humanity, for friendship between peoples, and for contributing to the creation of a better world.

Krainer is best known for his work on RNA splicing and the development of Spinraza®, the first FDA-approved treatment for spinal muscular atrophy (SMA). SMA is a neurodegenerative disease that is the leading genetic cause of infant death. For this research, Adrian was awarded the Jacob and Louise Gabbay Award in Biotechnology and Medicine, which recognizes scientists in academia, medicine, or industry whose work had outstanding scientific content and significant practical consequences in the biomedical sciences.


D. Tuveson

The Pew Charitable Trusts granted Adrian and his collaborator Paola Haeger Soto, an associate professor at the Universidad Católica del Norte in Chile, a $200,000 Innovation Fund grant. The researchers will investigate the biology behind fetal alcohol syndrome. The Pew Innovation Fund encourages cross-disciplinary collaborations to tackle biological questions in new ways.

Director of the CSHL Cancer Center David Tuveson was inaugurated president of the American Association for Cancer Research (AACR). Tuveson has dedicated his career to identifying new ways to diagnose and treat pancreatic cancer, a highly lethal disease. As AACR president, Tuveson will bring his distinguished scientific and clinical expertise in cancer to one of the oldest and largest cancer research organizations in the world.

Z. Lippman

J.E. Moses

H. Furukawa

T. Janowitz

This year, the National Cancer Institute (NCI) renewed the CSHL Cancer Center grant with a $4.5 million annual award. Led by David, the center explores the fundamental biology of human cancer. CSHL first received funding and NCI designation in 1987. Today, CSHL researches many cancer types, such as breast, prostate, leukemia, glioma, pancreatic, sarcoma, lung, and melanoma.

The National Academy of Sciences (NAS) elected Professor & HHMI Investigator Zach Lippman as a member. Members are chosen for their original and significant contributions to science and the world. Lippman has made major discoveries in plant genetics, studying the genes that control the size and yield of important crops.

The Royal Society of Chemistry awarded an international team of scientists the first-ever Organic Division Horizon Prize: the Robert Robinson Award in Synthetic Organic Chemistry. Professor and Fellow of the Royal Society of Chemistry John E. Moses received this award as a part of a collaborative effort with prestigious institutions around the world, including Nobel laureate K.B. Sharpless of Scripps Research Institute. The prize recognizes the development of multidimensional click chemistry, a groundbreaking and innovative technology that creates new kinds of molecules.

Professor Hiroyasu (Hiro) Furukawa received the 2020 Nakaakira Tsukahara Memorial Award from the Japan Neuroscience Society for his research on the NMDA receptor, a key molecule in the brain involved in various types of memory and is implicated in several. The award recognizes scientists conducting innovative research in the life sciences and was created in memory of Osaka University Professor Nakaakira Tsukahara, who studied flexibility, plasticity, and mechanisms of learning and memory in the brain.

Assistant Professor Tobias Janowitz and CSHL Fellow Semir Beyaz were two of the first-ever Endeavor Awards recipients from the Mark Foundation for Cancer Research (MFCR). The Endeavor Awards were created to unite scientists across diverse areas of expertise with the goal of addressing urgent questions in cancer research. Tobias and Semir are looking for systemic biological changes in the entire body after cancer develops.

Semir is also leading a multi-institutional team to generate a comprehensive atlas of uterine cells from patients of diverse ancestry. The $1 million project is part of the $28 million Chan Zuckerberg Initiative (CZI) Ancestry Network for the Human Cell Atlas initiative to identify and characterize uterine cells, in particular all the endometrial cells that line the uterus in people of African, Hispanic, Asian, and Native American descent.

The CSHL-led project, "Multi-omics Maps of Human Endometrium in Diverse Ancestries," is a partnership between the New York Genome Center (NYGC), Northwell Health, and Weill Cornell Medical College. The CZI project builds on the partnership already in place working on the NYGC-led Polyethnic-1000 initiative. That initiative was launched in 2018 to help address cancer care inequities in underserved populations. It is studying at least 1,000 ethnically diverse patients across the New York City population.

Assistant Professor Lucas Cheadle was selected as a McKnight Scholar for his work on microglia, a specialized class of immune cells in the brain. Cheadle and his team identified an important role for microglia in sculpting neural circuits in response to sensory experience. The award encourages neuroscientists in the early stages of their careers to focus on disorders of learning and memory, and is awarded for work that would have immediate and significant impact on clinically relevant issues.

Lucas was awarded a Klingenstein-Simons Neuroscience Fellowship for his research on the developing brain. This fellowship supports innovative research by early-career investigators and


S. Beyaz


L. Cheadle

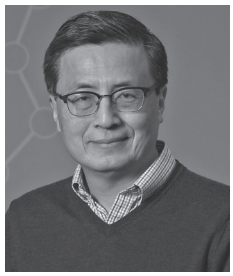

H. Meyer


J. Sheltzer

funds research into the mechanisms underlying a wide range of neurological and behavioral disorders.

Lucas also received the Rita Allen Scholar Award from the Rita Allen Foundation, which funds big ideas that aim to solve complex problems in science and civil society. Cheadle was selected for his neuroscience research.

UK Biobank awarded CSHL Fellow Hannah Meyer the Early Career Researcher of the Year Award for 2021. The award honors early-career researchers who have made significant scientific discoveries using UK Biobank's biomedical database. The award recognizes Meyer's study that examined the structure of the hearts of more than 18,000 individuals in the database.

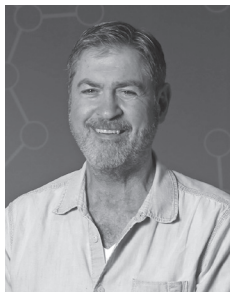

Z.J. Huang

CSHL Fellow Jason Sheltzer was awarded a TheoryLab Collaborative Grant from the American Cancer Society (ACS). TheoryLab™ is a new social media platform that allows cancer researchers to connect and launch collaborative projects. Sheltzer partnered with fellow TheoryLab™ user Rajan Kulkarni, an associate professor at Oregon Health & Science University, for this grant. Together, they are investigating whether having too many chromosomes affects how well cancer therapies work in melanoma patients.

Adjunct Professor Z. Josh Huang was awarded the National Institutes of Health (NIH) Director's Pioneer Award. The award supports scientists with highly innovative, "high-risk, high-reward" approaches to major challenges in biomedical, social science, and behavioral research. Huang was recognized for developing a new generation of precise cell engineering technologies to study the function of diverse cell types across animal organs and species. Josh credits the research program he started at CSHL two decades ago for making this award possible.


A. Moffitt

Senior Computational Fellow Andrea Moffitt was selected as a 2021 Leading Edge Fellow for her research on personalized genomic tools that help guide cancer therapies. Leading Edge is an initiative to improve gender diversity in the life sciences by providing women and nonbinary postdocs with a platform to present their work. She is the professional development chair of the Women in Science and Engineering (WiSE) group at CSHL.


D.A. Micklos

David A. Micklos, the founder and executive director of the DNA Learning Center, received the 2021 Bruce Alberts Award for Excellence in Science Education from the American Society for Cell Biology (ASCB). The award honors David for his innovation and leadership in science education at the DNALC, the world's first science center devoted to public genetics education. Each year, the ASCB recognizes individuals who have made significant contributions to the discipline and to the biology community over their careers.

I was awarded the 2021 Advance Global Impact Award from the Australian-based organization Advance.org. The annual prize honors an Australian who has had an extraordinary impact worldwide through their work; I was recognized for my cancer research using molecular biology and genetics, leadership, and influence in numerous fields and disciplines. The award was presented by


B. Stillman


A. Schorn


C. dos Santos


M. Egeblad


N. Bhattasali


D. Torre


S. Edwards


C. Prizzi

Professor Barry Marshall, the 2005 Nobel laureate in Physiology or Medicine and 2018 recipient of the Global Impact Award.

New Hires/Promotions

Andrea Schorn was promoted to Assistant Professor. Camila dos Santos was promoted to Associate Professor. Mikala Egeblad was promoted to Professor.

CSHL welcomed its first NeuroAI Scholar, Nikhil Bhattasali.

Douglas Torre joined CSHL as Vice President and Chief Information Officer. Shanique Edwards was recruited as Assistant Director, Research Operations.

Charles Prizzi was promoted to Senior Vice President & Special Advisor to the President.

Education Highlights

Meetings & Courses Program

CSHL hosted 28 virtual scientific meetings, six virtual advanced technology training courses, and two in-person courses this year. The Meetings & Courses Program has earned significant kudos within the scientific community by keeping alive the flame of scientific exchange during the COVID-19 pandemic. Attendance at the Laboratory's virtual meetings and courses was higher and more diverse than pre-pandemic levels because the virtual format eliminated space limitations and lowered the cost of participation. CSHL partnered with International Brain Research Organization, Chan Zuckerberg Initiative, and Regeneron to encourage broader participation from minority-serving institutions, low- and middle-income countries, and early-career scientists in need of financial aid.

Throughout the year, the scientific community expressed a strong interest in returning to the CSHL campus for in-person conferences and scientific training. The infrastructure to support this on-campus activity in the future is critical. Renovations to visitor housing begun during the pandemic are nearly complete, including conversion of cabins into family units and the addition of bathroom facilities. The Bush Lecture Hall has also undergone major renovation addressing some key design

The historic Bush auditorium, built originally in 1953, was newly renovated.

The new Bush fireplace room.

problems including noise abatement, lighting improvements, and new door and window hardware. At the Banbury Center, Sammis Hall was renovated to equip all bedrooms with private baths.

Banbury Center

The Banbury Center was closed to in-person meetings this year. Virtual options were unrealistic for most groups who value the Center's isolated and intimate setting for small meetings requiring deep discussion and productive workshops. The Center convened three virtual sessions to prepare for upcoming on-site meetings:

- *Environmental Consequences of Deep-Sea Mining* expert group met to (1) discuss the *scope* of comparisons between land-based and deep-sea mining; (2) review possible sources of *data*; and (3) propose *methodologies* for making comparisons. The expert group, excluding those still facing travel restrictions, will meet at Banbury in April 2022.

Sammis Hall blossoms

- *CSHL Technology and Education Council*, an advisory group of senior scientists who are members of the Laboratory's Corporate Sponsor Program, discussed diversity in clinical trials, indirect effects of COVID-19, and challenges of data. They helped develop themes for future Banbury Center meetings.
- *Making Career-Spanning Learning in the Life Sciences Inclusive and Effective for All* held a kickoff meeting to consider meeting objectives and start case study work on challenges faced by short-format trainers in the life sciences. An in-person meeting will take place in May 2022.

The Center celebrated three publications that resulted from prior Banbury meetings. Participants in the 2019 in-person and 2020 virtual meetings on *Bridging the Research-to-Practice Chasm in Digital Mental Health* published the "Banbury Forum Consensus Statement on the Path Forward for Digital Mental Health Treatment" in *Psychiatric Services*. The 2020 *MAVEN Project* leadership team produced "Introducing the MAVEN Leadership Training Initiative to diversify the scientific workforce" in *eLife*. The *Copper Cancer Consortium* published "Connecting copper and cancer: from transition metal signaling to metalloplasia" in *Nature Reviews Cancer*.

School of Biological Sciences

There were two U.S. and six international students in the twenty-third incoming class. By 2021, 127 students received their Ph.D. degrees from CSHL. One-third of our graduates are in faculty positions, with most of them in tenure-track positions at major U.S. or foreign research institutions. One-third work in industry. Other graduates are postdoctoral fellows, doing research in an academic setting, or are pursuing other scientific careers, such as university administrators, CEOs of biotech companies, and consultants. Applications for 2022 admissions were at a historic high.

The School secured a Postbaccalaureate Research Education Program (PREP) grant from the National Institutes of Health to start a new program for students from minority groups underrepresented in the sciences. The program is for recent graduates. Starting in 2023, four CSHL PREP postbacs will spend a year conducting research with a faculty member, attending courses, professional and skills development workshops, and preparing to matriculate into top-level graduate programs. With this program, CSHL now has undergraduate, postbac, and Ph.D. programs.

School of Biological Sciences entering class of 2021

All CSHL postdoctoral fellows and graduate students are now enrolled in a professional development initiative of the New York Academy of Sciences, the Science Alliance. The initiative is a consortium of universities, teaching hospitals, and independent research facilities in the New York City metro area. This year, CSHL supported a biannual conference, "What Can You Be with a Ph.D."

Because of the pandemic, the Undergraduate Research Program was conducted virtually this year. The Partners for the Future Program for high school students continues to grow with increased numbers of students, particularly from underrepresented communities.

DNA Learning Center

CSHL is the largest provider of biotechnology instruction at the precollege level in the United States. The DNA Learning Center (DNALC) engages more than eight million students across the globe in hands-on experiments with DNA. Together with the City University of New York (CUNY), CSHL opened the DNA Learning Center NYC (DNALC NYC) at the New York City College of Technology in Brooklyn on September 24, 2021. The 18,000-square-foot facility will serve 30,000 New York City middle- and high-school students annually, with a focus on engaging underrepresented communities. Two of the DNALC NYC lab classrooms are dedicated to college-level research courses specially designed for City Tech students. It is the newest and largest of thirteen CSHL DNALC teaching facilities in the United States.

DNA Learning Center (DNALC) Assistant Director Amanda McBrien was named in Crain's New York Notable Nonprofits and Philanthropy list. She was chosen for her work adapting the DNALC's programs to keep students learning hands-on science during the COVID-19 pandemic. The list recognizes people who have delivered innovative programs in response to safety concerns or other challenges in the wake of the pandemic, and Amanda pivoted the DNALC's educational programs to create a unique blend of online classes and at-home science kits.

A. McBrien

After a year of remote learning, DNALC rebooted in-person summer camps at 50% occupancy, including camps at DNALC NYC. With strong virtual camp attendance, total summer camp attendance was up by 14% over the previous year. School year field trips were severely limited by the pandemic. With the gradual relaxing and local

Newly opened CSHL DNA Learning Center NYC provides hands-on learning to students.

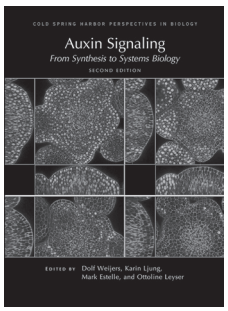
New York City's 110th Mayor Eric Adams cut the ribbon at the opening of the CSHL DNA Learning Center NYC.

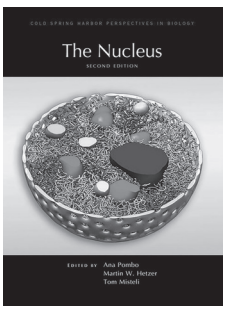
interpretation of CDC and local government guidelines, full classes of students from some Long Island school districts began to come back to the DNALC facility in Cold Spring Harbor.

Cold Spring Harbor Laboratory Press

CSHL Press published five new titles in 2021, four of them derivatives of the *Perspectives in Biology* and *Perspectives in Medicine* journals: *Influenza: The Cutting Edge*; *T-Cell Memory*; *Ahead of the Curve: Women Scientists at the MRC Laboratory of Molecular Biology*; *Auxin Signaling: From Synthesis to Systems Biology*; and *The Nucleus*.

The strong performance of our book program was driven by highly effective direct-to-customer marketing and e-commerce efforts. Offering electronic editions has helped drive this success: in 2021, more than 40% of Press website sales included an e-book, either as a companion to a print edition or a stand-alone purchase.





Editorially, CSHL's scientific journals continue to achieve recognition for high standards of quality and relevance. Judged by impact factor, *Genes & Development* and *Genome Research* remain highly positioned in their disciplines among primary research journals. Both journals continue to rank in the top 1% of the 9000+ journals in the Science Citation Index. *Perspectives in Biology* is in the top quartile of Cell Biology and *Perspectives in Medicine* in the top quartile of Research & Experimental Medicine.

Life Science Alliance is an open-access journal owned and published jointly by CSHL, the European Molecular Biology Organization, and Rockefeller University. Launched in April 2018, the journal published 198 new articles in 2021. Usage of the journal's content across all platforms grew more than 18% over the previous year.

Preprints in Biology and Medicine

A preprint is a research manuscript made freely available by its authors on a public website—a preprint server. The Laboratory's preprint server, bioRxiv, is the world's largest source of preprints in biology, with more than 148,000 unique manuscripts, increasing at a rate of more than 3,000 each month. In 2021, nearly 37,000 new manuscripts were posted.

bioRxiv contains the work of 580,000 authors with 45,000 institutional addresses in 151 countries and dependent territories. The largest subject categories are neuroscience (18%), bioinformatics (9%), and microbiology (9%). At least 70% of manuscripts posted to bioRxiv are published in a journal within two years: nearly 81,000 papers first posted to bioRxiv have been published in 4,000 journals.

medRxiv was launched in 2019 as a complement to bioRxiv. It is owned and operated by CSHL and managed in partnership with Yale University and BMJ, the global health information provider. Generous funding is provided by the Chan Zuckerberg Initiative.

As of February 15, 2022, 29,500 unique manuscripts were posted to medRxiv from 157 countries. The largest subject categories on medRxiv are Infectious Diseases (25%), Epidemiology (19%), and Public and Global Health (9%). Usage of medRxiv increased dramatically in 2020, rising to 10 million page views per month at its peak; it has maintained levels of 6–7 million views since then. More than 10,500 papers first posted to medRxiv have been published in more than 2,300 journals.

The COVID-19 pandemic proved that preprint servers are made for crises in public health when there is a need to share the newest information with utmost speed. There was a surge of pandemic-related submissions to medRxiv and bioRxiv that began before the pandemic was widely recognized. Some 22,000 such articles are now available.

Board of Trustees

In 1890, the Brooklyn Institute of Arts and Sciences established a program for biology teachers on Long Island Sound that became the modern-day CSHL. Eric Adams, New York City's 110th Mayor, welcomed CSHL back to Brooklyn in 2021. "This state-of-the-art facility will be a hub for hands-on STEM laboratory education for all New York City students, and a destination for families to learn about genetics, genealogy, and more," he said. Thirty million dollars was raised for the DNA Learning Center facility at City Tech of the City University of New York. Donors included founding contributor Laurie Landeau Foundation, Achelis and Bodman Foundation, Booth Ferris Foundation, Office of the Brooklyn Borough President, Carson Family Charitable Trust,

From *left* to *right*: CSHL President and CEO Bruce Stillman, Double Helix Medal recipients Leonard Schleifer and Reggie Jackson, Chair of the CSHL Board of Trustees Marilyn Simons, and Double Helix Medal recipient George D. Yancopoulos.

J. Moutoussamy-Ashe

E. Cogan Fascitelli

Ellen and Casey Cogut, William Randolph Hearst Foundation, Jerome Levy Foundation, Terry and Bob Lindsay, the Perkin Fund, Pfizer Foundation, Alison Holtzschue and Doug Schloss, Simons Foundation International, Alfred P. Sloan Foundation, Danielle and Paul Taubman, Thompson Family Foundation, and Anne Wojcicki Foundation.

The Double Helix Medals Dinner raised a record $5 million honoring baseball legend Reggie Jackson and Regeneron Pharmaceuticals, Inc. cofounders Leonard Schleifer and George D. Yancopoulos. The event was chaired by trustees Ms. Jamie Nicholls and Mr. O. Francis Biondi, Jr., Mr. and Mrs. Jeffrey Kelter, Mr. and Mrs. Robert Lindsay, Drs. Marilyn and James Simons, and Mr. and Mrs. Paul Taubman. The 20th annual Women's Partnership for Science luncheon, attended by 300 people, raised more than $250,000 to support women scientists' research. A $3 million gift established Chris Vakoc as the first Alan and Edith Seligson Professor of Cancer Research.

Philanthropic contributions are crucial to the Laboratory's success. We mourned the loss of three champions of CSHL, trustees David Knott, Alan Seligson, and Ed Travaglianti. Contributing fresh perspectives are new trustees: photographer and public health advocate Jeanne Moutoussamy-Ashe, and businesswoman and philanthropist Elizabeth Cogan Fascitelli.

Library and Archives

2009 Nobelist and former CSHL Fellow Carol Greider donated her 1975–1992 lab notebooks and data to the Archives, which has a mission to share the historic impact of life science on society. Greider won the 2009 Nobel Prize for work on telomerase, a protein linked to aging and cancer. She made her pioneering discoveries as a graduate student in Elizabeth Blackburn's laboratory at the University of California Berkeley in the 1980s and continued to study telomerase as one of the first CSHL Fellows.

More than 800 virtual attendees joined a virtual event on October 18 about the life in science of three prominent Nobel Prize laureates, Dorothy Crowfoot Hodgkin, Jennifer Doudna, and Elizabeth Blackburn. Presented by the Center for Humanities and the History of Modern Biology, the event was organized by Nancy Hopkins, Amgen Inc. Professor of Biology Emerita, Massachusetts Institute of Technology, Mila Pollock, Executive Director, CSHL Library &

Nobel laureate and CSHL alumna Carol Greider, circa 1985.

Archives, the Center for Humanities and the History of Modern Biology, and Jan Witkowski**,** Professor, CSHL School of Biological Sciences.

Susan Hockfield, president emerita of MIT, moderated the discussion with Georgina Ferry, biographer, author of *Dorothy Crowfoot Hodgkin: Patterns, Proteins and Peace, a Life in Science*; Jennifer Doudna, subject of *The Code Breaker: Jennifer Doudna, Gene Editing, and the Future of the Human Race* by Walter Isaacson; and Elizabeth Blackburn, co-author of *The Telomere Effect: A Revolutionary Approach to Living Younger, Healthier, Longer.*

Business Development and Technology Transfer

The first three quarters of 2021 proved to be a banner period for the biotech industry in raising capital and starting new companies. During this time, the Business Development and Technology Transfer team was able to close its largest-ever deal with an early-stage company (operating in stealth mode at press) to start up equity, provide five years of funding to access multiple drug targets, and, upon success, bring milestones and royalties to CSHL. This was very timely as biotech company valuations started to drop toward the end of the year.

Licensing and equity revenue received totaled $2.8 million and we received $0.55 million of patent reimbursement. Sponsored research booked in 2021 grew to $2.5 million on the back of the new deal mentioned above.

CSHL's science credentials in drug development were also recognized in the signing in 2021 of an institutional agreement with Autobahn Labs, a novel venture capital–backed early-stage accelerator company. The promise of this deal brings early-stage capital to fund drug development programs and advance new clinical assets to become investigational new drugs (IND). The first company to receive funding with this model is Lingbo Zhang's work on M4 inhibitors.

Fierce Biotech named Mestag Therapeutics™, a start-up inflammatory disease and immuno-oncology company, as one of its 2021 "Fierce 15" biotechnology companies. Mestag was founded in 2020 by an international team of researchers including Professor and Cancer Center Director David Tuveson. Mestag is developing new therapeutics for people affected by inflammatory disease and cancer. Tuveson and his colleagues target fibroblasts, the most common type of cell found in connective tissue. Mestag received $11 million in seed financing, jumpstarting its efforts to develop a first-in-class fibroblast therapeutic strategy in collaboration with CSHL.

CSHL spin-out company Envisagenics and Biogen Inc. announced a new collaboration to advance RNA research in central nervous system diseases by leveraging the Envisagenics artificial intelligence–based platform called SpliceCore®. Led by CEO Maria Luisa Pineda, who is a CSHL School of Biological Sciences alum, Envisagenics uses its proprietary algorithms to identify potential RNA splicing errors and design potential therapeutics to fix them. Biogen is a global biotechnology company that pioneers treatments for neurological diseases such as multiple sclerosis, spinal muscular atrophy, and Alzheimer's.

The SpliceCore® platform was developed by Martin Akerman when he was a postdoc in CSHL Professor Adrian Krainer's laboratory. Biogen and Ionis Pharmaceuticals collaborated with Krainer's team to release Spinraza®, the first FDA-approved treatment for spinal muscular atrophy, in 2016. Akerman, now co-founder and chief technology officer of Envisagenics, is using SpliceCore® to discover splicing errors and design treatments for other RNA splicing-related diseases.

CSHL is collaborating with Autobahn Labs, a new life sciences incubator, to catalyze the Laboratory's early-stage discovery programs into spin-out companies that commercialize transformational new therapies. CSHL is a world leader in basic biological research and in target discovery for human genetic diseases like cancer. Autobahn will provide up to $5 million to early-stage drug discovery projects that are beyond the academic funding model through its association with Samsara BioCapital, a leading life sciences investment firm, and Evotec SE, a global drug discovery

and development company. This collaboration will enable us to advance our basic biology expertise more quickly from the lab to the clinic.

Infrastructure

CSHL's Facilities Department worked on more than 70 capital projects during 2021.

Construction was completed on the new DNA Learning Center at City University of New York's City Tech facility in Brooklyn, New York. The grand opening was held at the 18,000-square-foot facility in September to kick off programming.

A full renovation and modernization of the 3,775-square-foot Bush Lecture Hall was completed in 2021. The stone patio space outside of Bush Lecture Hall and the Blackford Dining Hall was also replaced.

The revitalization of the 11 cabins for Meetings & Courses Program visitors approached completion. The newly renovated cabins will provide more than 12,000 square feet of renovated housing throughout the year.

The much anticipated rebuild of the historic Seawall on Cold Spring Harbor commenced in June. This project refurbishes approximately 1,300 linear feet of seawall. CSHL worked closely with regulatory agencies including the U.S. Army Corps of Engineers, New York State Department of Environmental Conservation, New York State Historic Preservation Office, and the Village of Laurel Hollow to design the new pile-supported concrete seawall with stone facia. Stones from the existing seawall were reused to maintain the historic integrity of the wall. The height of the wall is increased by 24 inches and is extended at both the north and south ends. Construction will be completed in 2022.

Vital housing renovations continued at the Easthouse Residence, Hershey House, and DeForest North and South locations on main campus and at Sammis Hall on the grounds of the Banbury Conference Center.

At Uplands Farms, construction of new state-of-the-art growth chambers continued, providing 288 square feet of growth area. The installation will be completed in the summer of 2022.

CSHL continued planning for a capital project to expand the facilities on the hillside of the main campus. Initial plans call for new laboratory buildings, housing for Meetings & Courses programs and other scientific visitors, and additional campus parking.

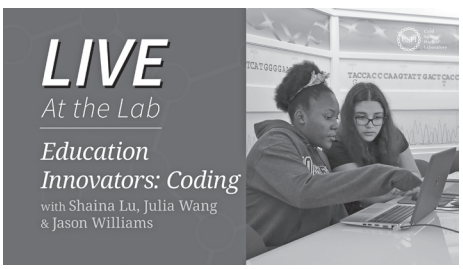
Construction underway on the historic CSHL seawall, summer 2021.

The Facilities Department completed an ASHRAE Level II Energy Audit in 2021 as part of the development of CSHL's energy and sustainability master plans. Programs to modernize and improve the heating, ventilation, air conditioning, electrical, and plumbing systems throughout facilities continue.

Community Outreach

COVID-19 health and safety restrictions limited in-person public programming at CSHL facilities. Virtual programming, the CSHL website CSHL.EDU, and social media channels continued to grow the institution's engagement with broader scientific and nonscientific audiences.

CSHL Public Presentations



January 5: Virtual Event: *Live @ the Lab Defeating Cancer: Working with Communities to Conduct Better Cancer Research* with Kevin Cassel, Dr.PH., Assistant Professor Population Sciences in the Pacific Program, University of Hawaii Cancer Center. Presented as part of the ongoing Roy J. Zuckerberg community engagement series from CSHL's NCI-designated Cancer Center.

March 24: Virtual Event: *Live @ the Lab: Adenovirus—A Look Back at Early CSHL Research* with Terri Grodzicker, Ph.D., CSHL Dean of Academic Affairs, and Bruce Stillman, Ph.D., CSHL President & Chief Executive Officer; moderated by Scientific American journalist and podcast host Steve Mirsky.

April 14: Virtual Event: *Live @ the Lab: Education Innovators*, with CRAIN'S award winner Amanda McBrien, Assistant Director, DNA Learning Center; moderated by CSHL Communications Department Creative Director Eliene Augenbraun, Ph.D.

April 28: Virtual Event: *Live @ the Lab: Education Innovators, CODING* with Shaina Lu, Ph.D. candidate, CSHL Women in Science (WiSE) Coding Camp Instructor, Julia Wang, Ph.D. candidate, CSHL WiSE Coding Camp Instructor, and Jason Williams, Assistant Director, External Collaborations, CSHL DNA Learning Center; moderated by Charla Lambert, Ph.D., Director of CSHL's Office of Diversity, Equity and Inclusion.

July 1: Virtual Event: *Live @ the Lab Panel Discussion about CSHL Programs and Experiences that Introduce Students to Biological Research*. Panelists included Diana Benedicto-Jimenez, Student, Paul D. Schreiber Senior High School, incoming class of CSHL Partners for the Future, Connor Fitzpatrick, Ph.D. candidate; Monn Monn Myat, Ph.D., Associate Dean, CSHL School of Biological Sciences; and Jason Williams, Assistant Director, External Collaborations, CSHL DNA Learning Center; moderated by Charla Lambert, Ph.D., Director of CSHL's Office of Diversity, Equity and Inclusion.

Social Media Outreach

In 2021, CSHL continued to grow its presence on social media by utilizing Facebook, Twitter, Instagram, and LinkedIn to engage the broader scientific and nonscientific audiences in research and education program developments. Through the daily promotion of stories about science, scientists, educators, and the campus community, CSHL's channels successfully grew from 2020:

Facebook reached 24,000 followers, Twitter followers grew by 20% to 33,000, Instagram followers totaled 4,000, and LinkedIn reached 11,000 followers. The CSHL monthly email newsletter achieved 10,000 subscribers.

Looking Forward

In 2021 CSHL achieved historic milestones in its research and education programs, highlighting the importance of strategic investments in strong physical and intellectual foundations that facilitate future growth and evolution.

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