Research

How Jumping Genes May Contribute to Age-Related Brain Degeneration

Cognitive decline is often obvious to people as they age. However, corresponding changes in the brain, at a molecular level, are not well understood. This year, Associate Professor Joshua

Dubnau and his colleagues used the fruit fly brain as a model to offer insight into a possible molecular basis of neurodegeneration. They identified a class of DNA elements, known as transposons or "jumping genes," that become more abundant and active as the brain ages and cognitive function declines. Transposons are short repetitive sequences of DNA that insert themselves into an organism's genome. When active, transposons copy themselves and jump into other locations within the genome. After the initial stages of life, transposons are typically inactive, but Dubnau and his team discovered that as flies age, transposons become more active and move. A protein called Ago2 is important for regulating transposon levels. When Ago2 is mutated in young flies, transposon levels prematurely increase. At the same time, long-term memory declines, mirroring the memory defects seen in much older flies. Dubnau's work suggests that this "transposon storm" may be responsible for age-related neurodegeneration—a hypothesis his lab is actively working to test.



When researchers and clinicians think of targeted cancer drugs, they are generally looking for therapies that will directly attack tumor cells and spare nearby healthy cells. But new research from Assistant Professor Mikala Egeblad and Associate Professor Scott Powers challenges that strategy. They found that tumors rely, at least in part, on multiple signals from healthy cells in the local environment to promote growth. Egeblad, Powers, and their team systematically cataloged the repertoire of interactions between breast cancer cells and a type of healthy cell that is commonly found in breast tissue. They used genomic analysis to identify 42 different factors that are released by normal cells, the majority of them encouraging cancer growth. They found that each factor came with a different set of instructions for the tumor. Looking closely at three of these factors, the team discovered that one promoted survival, another signaled for greater proliferation, and a third increased inflammation and the growth of nearby blood vessels supporting tumor development. The team blocked these signals, alone and in combination, and found that targeting multiple factors did the most to inhibit tumor growth. Their work has broad implications for future cancer drug development. The most effective cancer therapies, the work suggests, would combine two kinds of drugs: those that target tumors and those that block proliferation signals from nearby healthy cells.



J. Dubnau



S. Powers

Natural Mutations Point the Way to Greater Corn Yield

As the global population soars beyond 7 billion, efforts to increase food production have taken on new importance. This year, Professor David Jackson and his colleagues made discoveries that offer insight into how to naturally boost the production of maize, a staple of the world diet. Known commonly as corn kernels, the edible parts of a maize plant are the seeds. These seeds, like all organs in a plant, are derived from a structure known as the meristem. Jackson began with a simple hypothesis: Increasing the size of the meristem could create more area for kernels to develop and thus lead to an increase in the plant's yield. To test this hypothesis, Jackson and his team sought



D. Jackson



A. Kepecs



J. Huang

to identify genes that control the size of the meristem. They discovered a mutation in one of these genes, known as *FASCIATED EAR2* (*FEA2*), that results in a larger meristem. Plants grown with the *FEA2* mutation produce ears of corn that have a greater number of rows and up to 13% more kernels than their normal counterparts. In other experiments, Jackson and colleagues identified another mutant gene, known as *COMPACT PLANT2* (*CT2*), that also regulates the size of the meristem. The team explored the molecular basis of these mutations and discovered that the *CT2* gene encodes for a protein known as G α that unexpectedly interacts with FEA2, an unusual type of cell-surface receptor. Detailed understanding of these natural mutations and their impact on plant growth points the way to higher maize yields—good news if we are to meet the planet's ever-growing food needs.

Brain Uses Disinhibition to Obtain Extremely Precise Control

There are two major classes of neurons in the cerebral cortex: excitatory and inhibitory. Assistant Professor Adam Kepecs and his team are working to understand how signaling between these neurons shapes mental processes such as cognition and learning. This year, Kepecs and his team identified the role of a special class of inhibitory neurons, known as VIP neurons, in the cortex. In collaboration with CSHL Professor Josh Huang, they used a technique known as optogenetics to specifically stimulate VIP neurons in the mouse brain. They found that when these neurons are active, signaling from certain neurons decreases, whereas the activity of other neurons increases. Upon closer investigation, Kepecs and his colleagues discovered that VIP neurons were inhibiting other inhibitory neurons in the brain, which allowed the excitatory neurons to become more active. This process, known as disinhibition, is something like releasing the brakes on a car without stepping on the gas pedal. Excitatory neurons are not directly activated, which gives the brain highly precise control over cortical processing. Kepecs and his team found that VIP neurons function in the auditory cortex and mediate reward and punishment behaviors. In linking neuronal signaling with a behavior, Kepecs has gained critical insight that will allow him to further explore the complex networks that control cortical function.

First Animal Model of Adult-Onset Motor Neuron Disease, SMA

Spinal muscular atrophy (SMA) is a rare but devastating motor neuron disease. It is caused by a defect in a type of genetic editing, known as splicing. The splicing error occurs in a gene, called *SMN1* (survival of motor neuron 1), that is required for motor neurons to function and lowers the amount of SMN protein in the body. In its most severe form, the disease affects infants and young children; it is the leading genetic cause of childhood mortality. Patients with more SMN protein and, therefore, more mild manifestations of the disease, can live to adulthood,

but they develop debilitating handicaps such as losing the ability to walk. Professor Adrian Krainer, an authority on splicing, has made major contributions to the study of the most serious forms of SMA, and he has taken part in work leading to the discovery and testing of a promising drug, currently in Phase-2 clinical trials. Yet, the adult-onset form of SMA has been challenging to research because scientists have lacked a proper animal model. This year, Krainer led a team to develop a mouse model for adult-onset SMA, which faithfully reproduced many of the pathologies seen in patients. His team was particularly interested in understanding how SMN1 protein levels affect neuronal function in adults. They were excited to discover that only moderate levels of the protein are needed, suggesting that clinicians will have a broad time window in which to treat adult patients with SMA.



A. Krainer

Mathematical Technique to Declutter Cancer Cell Data

In recent years, next-generation sequencing has brought genome-wide data to clinical research, paving the way for major new discoveries in the diagnosis and treatment of disease. Despite this promise, there has been some significant challenges. Sequencing generates extremely large data sets that cannot easily be interpreted. Advanced computing technology is required to extract meaningful information from the data. This year, Assistant Professor Alexander Krasnitz and Professor Michael Wigler developed a mathematical method of simplifying and interpreting genome data based on variations in the sequence. These changes in genomic sequence are common in diseases such as cancer, where certain segments of DNA may be amplified or deleted in a tumor cell. These mutated regions are called "intervals" and may appear repeatedly within a specific population of cells. When the intervals are superimposed against a map of the full human genome, they form "stacks" at discrete locations. Because of the vagaries of collecting genome data and a certain amount of small-scale variation in the precise boundaries of the deleted or amplified DNA intervals, these stacks are wobbly. This makes them very hard to accurately interpret. Krasnitz and Wigler devised a mathematical method called CORE to clean up the stacks of overlapping data, revealing a rich structure underlying all of the clutter. Such analysis is a potentially valuable guide to prognosis and can also help to make important treatment decisions.



A. Krasnitz



M. Wigler

Finding Where Fear Memories Form in the Brain

Fear elicits a similar response in animals and humans: a momentary feeling of paralysis as the brain assesses present danger. This past year, Assistant Professor Bo Li examined how this universal emotion is learned, controlled, and remembered, and how the brain translates fear into action. Li and his team trained mice to be afraid of an auditory cue. They used a technique called opto-

genetics to activate specific neurons with laser light, directed fiberoptically into the brain with pinpoint accuracy. They could then record changes in the behavior of the mouse to determine how stimulating a particular area of the brain results in action. Li's team found that fear conditioning alters the release of neurotransmitters in a part of the brain called the central amygdala. The central amygdala is associated with emotion, pain processing, and reward-based behavior. The team further examined this portion of the brain and discovered that both formation and recall of fear memory requires the activation of a specific class of neurons, known as somatostatin-positive neurons, within the central amygdala. This work demonstrates that specific subsets of neurons in the central amygdala have an active role in the brain's fear response, converting fear into action. Li's lab hopes to build on these discoveries to understand the neural circuit changes involved in posttraumatic stress disorder (PTSD).

Genetics Explains Variable Severity of Birth Defects in EEC Syndrome

Cleft palate can be part of a larger condition known as ectodactyly, ectodermal dysplasia, clefting syndrome (EEC), that can be debilitating and sometimes fatal. The illness is caused by a well-known DNA mutation in the p63 gene, but the birth defects that result range in severity. In fact, not all children with the p63 mutation develop EEC. This year, Professor Alea Mills and her team discovered a genetic modifier of the p63 mutation that explains how two people with the same mutation can manifest the illness very differently. They engineered a mouse in which the normal copy of p63 was replaced with the mutated version seen in EEC. These mice developed with birth defects ranging in severity, similar to babies with EEC. A complex series



B. Li



A. Mills

of genetic experiments revealed that the presence or absence of one variant type of the p63 protein, called TAp63, determines whether or not a child with the p63 mutation will actually develop EEC pathology. Loss of TAp63 alone does not cause EEC. But when mice lacking TAp63 also possess the EEC-causing p63 gene mutation, pathology always occurs. This work suggests that in children who have inherited the EEC-causing mutation from one of their parents, levels of the TAp63 protein determine whether and to what extent these children will be born with birth defects. Mills speculates that when levels of TAp63 drop beneath a certain threshold, it is no longer protective, opening the way to pathology. The next step for researchers in this area is to compare the DNA of children only mildly affected by EEC with siblings or other children who have a severe form of the disease.

Linking Brain Cell Activity with Smell Recognition and Behavior

An orange and a grapefruit have quite similar odors; at the same time, they are both sweet and acidic. Despite the similarity, our brains can readily differentiate between the two. Associate



G. Turner

Despite the similarity, our brains can readily differentiate between the two. Associate Professor Glenn Turner and colleagues have made significant advancements this year using the fruit fly olfaction system to identify how the brain distinguishes one scent from another. The fruit fly brain has a structure called the mushroom body that is responsible for learning and memory, including olfaction. Within the mushroom body are neurons called Kenyon cells that have unique response properties. Signals from these neurons are rare and often weak. To determine if and how Kenyon cells function in odor memory, Turner and his team used an imaging technique that allowed them to monitor and measure the response of more than 100 Kenyon cells at once. They found that their sparse responses allow these neurons to integrate multiple signals that provide a large amount of information about a particular odor. They discovered that as few as 25 neurons are required to distinguish among similar scents. This informa-

tion will help Turner's team to better understand how the brain combines sensory data to make decisions.

Growth Factors Contribute to Drug Resistance in Pancreatic Cancer

Pancreatic cancer is one of the most deadly and intractable forms of cancer, with a 5-year survival rate of only 6%. New treatments are urgently needed. This past year, Professor David Tuveson



D. Tuveson

uncovered a new avenue for drug development. It is thought that many existing chemotherapies fail because they are unable to reach the interior of pancreatic tumors. Tuveson and his colleagues tried to address this problem by targeting high amounts of a chemotherapy drug directly into the tumor. Unfortunately, the response did not improve, suggesting that other factors contribute to tumor survival. The team discovered proteins, known as growth factors, that promote tumor growth in the pancreatic tumor mass. Using an antibody against just one of these factors, called connective tissue growth factor (CTGF), the team was able to block nurturing signals in the local tumor environment. When mice with pancreatic cancer were treated with both the antibody and standard chemotherapy, tumor cells died and mice lived longer. Tuveson's work suggests that these growth signals within the tumor overome the power of conventional chemotherapies.

New drugs targeting these survival signals might be used in combination with existing chemotherapies to stop cancer growth.

Scientific Advisory Committee

We are honored to receive input from scientific world leaders who serve on CSHL's Scientific Advisory Council (SAC). The SAC is a nine-member Council that also includes participation

from CSHL Trustee James M. Stone, Ph.D., and CSHL Scientific Trustee Michael R. Botchan, Ph.D. Chairing the SAC is Fred Alt, Ph.D., of Harvard University Medical School. Other members include Drs. Cori Bargmann, Joanne Chory, Carol Greider, Leonid Kruglyak, Markus Meister, Kevan Shokat, and Max Wicha.

Technology Transfer

As CSHL's employee numbers and operating budgets have grown significantly in the first decade of the millennium, so have opportunities for commercialization of our research discoveries and technologies. This year, CSHL announced the recruitment of Teri Willey to the new position of Vice President, Business Development and Technology Transfer. Teri brings a wealth of experience from leading transfer and business development for Mount Sinai Medical Center and the founding of several ventures including Cambridge Enterprise Ltd. and ARCH Development Partners.



T. Willey

John Maroney, who for the past 20 years has helped many CSHL investigators launch successful technology start-ups and negotiate licensing agreements, continues in his role as the Laboratory's general counsel. John played a critical part in the establishment of the Broad Hollow Bioscience Park, a collaborative biotech incubator that CSHL helps to lead on the campus of SUNY Farmingdale, the original home of the CSHL spin-off and cancer drug manufacturer OSI Pharmaceuticals Inc. (now owned by Astellas Pharma Inc.).

CSHL is engaged in technology transfer as one way of delivering important discoveries to the public. We are ramping up support to our scientists in partnering with companies, investors, and others to achieve this mission. This support includes identifying science ideal for partnering, finding the best partners, performing good negotiations, managing the corresponding transactions, and developing the team to carry out this work. 2013 was a year to take stock and initiate program changes in order to move forward with a new approach. 2014 will be a year for evolving the program, building the team, and completing new deals with industry.

Cold Spring Harbor Laboratory Board of Trustees

The CSHL Board of Trustees elects members whose academic and professional accomplishments reach beyond the boundaries of science, providing well-informed governance in an increasingly complex fiscal and regulatory environment. The Board welcomed four new trustees: Cornelia I. Bargmann, Ph.D., Jeffrey E. Kelter, Robert W. Lourie, Ph.D., and Thomas A. Saunders III.

The Board congratulated two retiring members, Scientific Trustee Dr. David Botstein and Alan Seligson. Dr. Botstein was the 2013 recipient of the Breakthrough Prize in Life Sciences and donated \$100,000 of his prize to CSHL to support its advanced technology courses. Mr. Seligson, who was named an Honorary Trustee, established the Andrew Seligson Clinical Fellowship in



C.I. Bargmann



J.E. Kelter





T.A. Saunders III

memory of his son who died of cancer, helping to set the stage for CSHL's Cancer Therapeutics Initiative.

The entire community mourned the passing of trustees and friends Colton Packer Wagner, Arthur M. Spiro, and Kathryn W. Davis.

Development

Together, the Board, the CSHL Association, the Corporate Advisory Board, and many individual foundations and donors raised more than \$6.9 million in unrestricted funds for research and education programs. Thanks to all those who contributed, especially the Charitable Lead Annuity Trust under the Will of Louis Feil and The Simons Foundation for new major gifts.

CSHL is grateful to the Lustgarten Foundation and Roy Zuckerberg for supporting the Cancer Therapeutics Initiative (CTI) and its leaders, including Dr. David Tuveson, an M.D./Ph.D. expert in pancreatic cancer. Infrastructure for the CTI is essential, and with help from David Koch, New York State Empire State Development, and an anonymous donor, construction of the Preclinical Experimental Therapeutics Facility began in November. The project is moving forward on the strength of a \$2 million award from Governor Andrew M. Cuomo's Regional Council initiative.

The Governor praised the initiative. "This expansion project demonstrates how Long Island is becoming a leading hub for scientific and medical study," Cuomo said. "With the support of the Regional Council Initiative, CSHL is moving forward with a facility that will enable critical research seeking to advance the quality of healthcare around the globe. I am pleased that the project is now under way and look forward to seeing its positive impact on the region for years to come."

Long Island Regional Economic Development Council Cochairs Kevin Law, President, Long Island Association, and Stuart Rabinowitz, President, Hofstra University, said, "This groundbreaking is a major milestone not only for Cold Spring Harbor Laboratory and Long Island, but also for the critical research CSHL conducts to find new and innovative ways to treat cancer and improve the quality of life for people around the world."

With dedicated state-of-the-art facilities and staff, CSHL will accelerate research aimed at developing new therapeutics for cancer and neurological disorders. Other significant contributors included the estate of Robert B. Gardner, Jr., Lisa Lourie and Dr. Robert Lourie, and the St. Giles Foundation.



CSHL Association Board of Directors



Groundbreaking of Preclinical Experimental Therapeutics facility

CSHL is extending the reach of its science education programs to urban centers all over the world. A new flagship center in Manhattan will serve as the nucleus for DNA learning in New York City. Middle and high school students will have access to hands-on DNA laboratory experiences to gain a greater understanding of their own uniqueness, the implications of personalized medicine, and their shared genetic heritage in America's melting pot. The NYC center has been made possible by a lead contribution by CSHL Trustee Laurie L. Landeau and significant gifts by the Thompson Family Foundation and the Alfred P. Sloan Foundation.

Unveiled this year was a commemorative wall honoring the major donors, who, under the leadership of Board Chairman Eduardo Mestre, contributed to the Hillside Campaign of 2003–2008. This campaign made possible the 2009 opening of six new Hillside Laboratory buildings, representing the largest expansion in the history of the Laboratory. With these research buildings, CSHL increased its research capacity by 40%.

Supported by our trustees, fund-raising events including the eighth Double Helix Medals Dinner (DHMD) in Manhattan opened CSHL's doors to many new friends in the New York metropolitan area. The DHMD honors individuals who have raised public awareness of the significance of biomedical and genetics research. We saluted Robin Roberts for her courage and tenacity in using her celebrity to share information about breast and blood cancers.



Commemorative wall, Hillside campus



Double Helix Medal winners P. Neufeld, R. Roberts, and Barry Scheck with Bruce Stillman

This year's DHMD also highlighted the impact that CSHL has had in leveraging biomedical technology for applications to benefit society. Since 1992, the Innocence Project has used DNA technology to generate evidence leading to the exoneration of 312 wrongfully convicted individuals. This is a concept that cofounders (and 2013 DHMD medal winners) Peter Neufeld and Barry Scheck advanced after attending a conference on the subject organized at CSHL's Banbury Center in 1989. The Banbury Center's role as a think tank bringing science and public policy experts together is unrivaled.

Research Faculty

Awards

- Professor and Howard Hughes Medical Institute Investigator Gregory Hannon won a MERIT (Method to Extend Research in Time) Award from the National Institute of General Medical Sciences. This prestigious award recognizes highly productive scientists by extending funding for an existing research project grant. A leader in the field of small RNA biology, Hannon has sought to understand the biological roles of small RNAs and the underlying mechanisms through which they operate.
- Professor Partha Mitra, Crick-Clay Professor of Biomathematics, was honored with two awards: the George S. Axelby Outstanding Paper Award of the Control Systems Society of the Institute of Electrical and Electronics Engineers (IEEE) and an INSPIRE (Integrated NSF Support Promoting Interdisciplinary Research and Education) grant from the National Science Foundation (NSF). The INSPIRE grant was established in 2012 to address some of the most complicated and pressing scientific problems that lie at the intersections of traditional disciplines. Mitra is weaving together theoretical threads from physics and engineering to arrive at a coherent theoretical framework for understanding connectivity and dynamical behavior of circuits in the mammalian brain. He is applying insights from his theoretical work to the Mouse Brain Architecture Project, with the goal of generating brain-wide maps of interregional neural connectivity.
- Associate Professor Adam Kepecs received the Memory & Cognitive Disorders Award from the McKnight Endowment Fund for Neuroscience, which provides support to encourage breakthroughs in understanding complex systems involved in neuron signaling.
- Assistant Professor Hongwu Zheng was the recipient of the Distinguished Scientist Award from the Sontag Foundation. He is investigating how brain tumors known as malignant glioma emerge from normal neuronal cells and transform into metastatic tumors.
- Four CSHL postdoctoral neuroscientists won NARSAD Young Investigator Awards from the Brain and Behavior Research Foundation. This support is intended to facilitate the transition for young scientists to ultimately work in laboratories that they themselves direct. Three of the CSHL awardees are studying autism spectrum disorder: Guy Horev, Yongsoo Kim, and Keerthi Krishnan. Sandra Aherns is conducting research on schizophrenia.
- Cited for her postdoctoral work in genetics and genomics, Research Investigator Emily Hodges was named one of five finalists in the annual Regional Blavatnik Award for Young Scientists.
- Postdoctoral Fellow Christine Iok In Chio was named a Damon Runyon Fellow in cancer research. As part of the Lustgarten Foundation Pancreatic Cancer Research Laboratory at CSHL, she is evaluating the biological role of oxidative stress in pancreatic cancer.

New Faculty

Welcome to our new CSHL Fellow Lingbo Zhang, Ph.D., who earned his doctorate in 2013 in a joint program of Massachusetts Institute of Technology and the National University of Singapore. CSHL Fellows direct their own research programs under the guidance of a senior faculty member. They have their own laboratory space and technician, as well as access to all of the Laboratory's core facilities. Fellowship appointments are for 3 years. Dr. Zhang is interested in understanding the self-renewal mechanism of stem and progenitor cells in the blood-forming system, work he hopes will lead to better treatments for a broad spectrum of unresponsive anemias associated with certain bone marrow failure disorders, myelodysplastic syndrome, and kidney disease. His work can also be applied to leukemic cells, a population of malignant cells whose self-renewal machinery has been hijacked.

Promotions

On January 1, 2013, Alex Gann began his appointment as Dean of the Watson School of Biological Sciences. Congratulations to Adam Kepecs, Bo Li, and Zachary Lippman, who were promoted to Associate Professor. Michael Ronemus was promoted to Research Assistant Professor.

Departures

Professor Lincoln Stein is now Program Director, Informatics and Biocomputing at the Ontario Institute for Cancer Research (OICR).

Education Programs

Banbury Center

In its 36th year, the Laboratory's think tank for science and public policy known as the Banbury Center was an exceptionally busy place. A total of 23 meetings were held, inviting more than 700 participants from 40 states and 20 countries. Approximately one-fifth of the attendees were from overseas and about one-third were women.

One of the year's highlights was a meeting called *Redesigning Photosynthesis: Identifying Opportunities and Novel Ideas* that brought plant biologists together to consider whether the efficiency of solar energy capture by plants might be improved. A fine example of a meeting on an "emerging topic"—something for which Banbury is known—convened a distinguished group to discuss whether transposable genetic elements might be active during normal neurogenesis, the process by which new neurons are generated. Until now, "jumping genes" have been known for their role in causing pathology.

A 2010 WSBS graduate, Yaniv Erlich, now on the faculty of the Whitehead Institute, organized a Banbury meeting to discuss strategies for maintaining privacy of data gleaned from genomes and other bioscience data sets. *Accelerate Genomic Research with Privacy Protections* included participants across disciplines from science to cryptography to ethics.

The Banbury Center also hosted three Watson School of Biological Sciences (WSBS) courses and six courses conducted as part of the Laboratory's Meetings & Courses Program. The Center appreciates support from numerous corporate sponsors and underwriters who helped to make its rich offerings possible.



L. Zhang



A. Gann



Z. Lippman



M. Ronemus

DNA Learning Center

This past year, some 20,960 students made field trip visits to DNA Learning Center (DNALC) facilities in Cold Spring Harbor, Lake Success, and Harlem. An additional 10,200 students were reached through in-school instruction by DNALC staff. There were also 1640 in-school lab exposures via mobile "Footlocker Kits" used by teachers in their own schools. These teachers previously received specialized DNALC training.

During the summer, 60 week-long biology and genetics summer camps were held in Cold Spring Harbor and eight other locations in New York, Massachusetts, and Connecticut, drawing a record 1240 students. Monthly *Saturday DNA!* sessions drew hundreds more children, parents, and grandparents.

At its main facility in Cold Spring Harbor, the DNALC this year updated museum space that currently features an exhibit on "Our Common Human Origins." More than 100 classes per year take an instructor-guided tour of the museum, which is also open to the public.



In its second year, the Center's innovative Urban Barcode Project (UBP) scored major successes, with teams of motivated NYC high school students competing, many from ethnic groups underrepresented in science. Fifty-three teams comprising 144 students were accepted into the competition and completed field work, wet labs, and bioinformatics analyses with the support of their teachers and UBP staff at Open Labs at Harlem DNA Lab. Teams presented their results at symposia at the American Museum of Natural History, with the grand prize awarded to Hostos-Lincoln

Academy of Science students Kavita Bhikhi and Hillary Ramirez, who investigated ant diversity in the Bronx.

The *BioMedia* team of the DNALC is award winning and trend setting. Their *3D Brain* iPhone app, launched in 2009 and available on multiple platforms, has been downloaded more than 2.2 million times, and it is used not only by teachers and students, as intended, but also by health professionals, patients, and the public. A 2013 iOS update provides current information about 29 primary structures of the human brain.

This year, the BioMedia team introduced live streaming and webinar programs, broadcast from the DNALC's Laurie J. Landeau Multimedia Studio. Altogether, approximately 4.9 million visits were recorded to the DNALC's 22 websites in 2013. DNALC-produced *YouTube* videos drew more than 823,000 views, with apps downloaded 579,163 times. Total visitation therefore numbered a record 6.26 million.

Since 1995, more than a dozen programs worldwide have been modeled directly on the DNALC experience. These centers, across America and in Europe, Asia, and Australia, provide hands-on experiments to more than 150,000 students annually. The DNALC is the largest provider of teacher training in molecular and genomic biology, and it is the only institution capable of offering high-



DNA Learning Center dedication, Notre Dame University

quality biochemical and bioinformatics instruction anywhere in the world. In the fall, a dedication ceremony marked the opening of the latest DNA Learning Center at Notre Dame University. The DNALC also continued to develop its relationship with Beijing No. 166 High School in China.

Plans to develop a new full-service DNALC teaching facility in Manhattan received a jump start with the receipt of a \$3 million start-up grant from the Alfred P. Sloan Foundation and a \$10 million endowment grant from the Thompson Family Foundation. These add to a lead endowment grant of \$6 million from CSHL trustee Laurie J. Landeau.

Meetings & Courses Program

With its beginnings in the first annual meeting, in 1933, of the Cold Spring Harbor Symposium on Quantitative Biology—a scientific conference series still going strong—the Meetings & Courses program in the last year attracted more than 11,600 participants. This included upwards of

7200 individuals who attended scientific meetings and more than 1300 trainees, teaching, and support faculty who took part in courses. An additional 3000 scientists from the Asia/Pacific region attended 17 conferences and one summer school held by the Cold Spring Harbor Asia program in Suzhou, China.

A major feature of CSHL meetings is that there are very few invited speakers. Meeting organizers select talks from abstracts submitted in advance, ensuring that the latest findings are presented and that young scientists have a chance to describe their work. Several meetings are held annually, including *The Biology of Genomes* and *Retroviruses*, but the majority of meetings convene every other year.

A total of 27 academic meetings were held in 2013. The 78th session of the historic Symposium series addressed Immunity and Tolerance and attracted almost 400 participants. The year saw the introduction of several successful new meetings: *Wiring the Brain, Metabolic Signaling and Disease,* and *Behavior and Neurogenetics of Nonhuman Primates.* Two special meetings, *Genes & Diagnostics: A Myriad of Issues in Biotech IP* and the *History of Restriction Enzymes,* drew rather different audiences of lawyers and historians, respectively.



78th CSH Symposium

The Courses program covers a diverse array of topics in molecular biology, neurobiology, structural studies, and bioinformatics. The primary aim is to teach professional scientists the latest advances that can be immediately applied to their own research. Increasingly, many courses feature a strong computational component as biology grows ever more interdisciplinary, incorporating methodologies from computer science, physics, and mathematics. Instructors, lecturers, and assistants come from universities, medical schools, research institutes, and companies around the world to teach at CSHL.

Grants from a variety of sources support the courses, with core funding provided by the Howard Hughes Medical Institute. The courses are further supported by awards from the National Institutes of Health and the National Science Foundation, private foundations, and other sources. Equipment and reagents are loaned or donated by companies, ensuring that the courses offer training in the latest technologies.

Cold Spring Harbor Laboratory Press

CSHL Press published a single volume in 1933, based on the Laboratory's first Symposium on Quantitative Biology. Since then, the Press has developed a program consisting of seven successful journals, 190 books, and two online services. It is now a digital publisher with a capacity for print production on demand, and in recent years, its staffing, skills, and organizational structure have been reshaped to this end.

In the United States and Europe, budgetary restrictions continued to squeeze research departments and the academic libraries that are the most important purchasers of scientific information. The Press weathered these pressures by maintaining first-class editorial standards and finding fresh ways of promoting its publications to scientists and their institutions worldwide. Examples include three review journals launched in the past 6 years and growth of subscriptions in emerging scientific communities abroad.

Widely cited impact-factor measurements place two Press journals, *Genes & Development* and *Genome Research*, in the top 1% of the 8000 journals in the *Science Citation Index*. Online usage of

these and their sibling journals continues to climb, exceeding 12 million full-text article downloads in 2013, an increase of 25%. *Cold Spring Harbor Protocols* and *Learning & Memory* continued to gain ground. *Cold Spring Harbor Perspectives in Biology* had particularly sharp growth, a vote of approval for its fresh approach of melding journal and book publishing. Testament to its editorial quality was the award of the Nobel Prize in 2013 to three scientists (Drs. Thomas Südhof, Randy Schekman, and James Rothman) who have edited recent *Perspectives* titles.



bioRxiv.org website

Watson School of Biological Sciences

The Press published 18 new book titles in 2013. Several were new editions of past best-sellers, including Antibodies: A Laboratory Manual and Lab Math: A Handbook of Measurements, Calculations, and Other Quantitative Skills for Use at the Bench. Eleven books were generated from the two online Perspectives review journals.

In November, bioRxiv, a new preprint service for the life sciences, was launched to permit distribution of scientific manuscripts not yet published in peer-reviewed journals. This enables researchers to establish priority for their work and to benefit from critiques offered by readers as manuscripts are honed for conventional publication in a peer-reviewed journal. bioRxiv provides an exciting platform on which to build other valuable services in future.

Under the leadership of its new Dean, Dr. Alexander Gann, the Laboratory's Ph.D.-granting program welcomed its 15th incoming class and graduated its 10th. Eight WSBS students were awarded Ph.D. degrees, bringing the total since the school's inception to 66.

Honorary degrees were conferred upon Jack E. Dixon, Ph.D., Howard Hughes Medical Institute Vice President and Chief Scientific Officer and Professor at the University of California, San Diego; and Brigid L.M. Hogan, Ph.D., F.R.S., Professor and Chair of the Department of Cell Biology at Duke University.



2013 WSBS graduates and honorary degree recipients

The 19th Annual Gavin Borden Visiting Fellow Lecture, reception, and dinner were held on October 28. Sean Carroll, Ph.D., delivered the lecture, titled "Brave Genius: A Scientist's Journey from the French Resistance to the Nobel Prize." Dr. Carroll leads the Department of Science Education of the Howard Hughes Medical Institute, the largest private supporter of science education activities in the United States, and is the Allan Wilson Professor of Molecular Biology and Genetics at the University of Wisconsin.

In August, the WSBS welcomed 10 new students. Members of the Class of 2013 were selected from among 274 applicants and represent the United States, Bulgaria, India, Israel, Italy, and Mexico. Other new graduate students entered as visitors from other institutions, including seven from Long Island's Stony Brook University; other current visitors hail from more distant institutions, including several in Germany, France, and Spain.

The achievements of the graduate program continued to grow. Scientific papers published by students appeared in major journals, bringing the cumulative total of WSBS student publications to more than 230. Current and former students won prestigious and highly competitive scholarships and fellowships. Watson School students continued to graduate considerably faster than students at comparable institutions and demonstrated an ability to secure excellent jobs. Fifteen WSBS graduates have thus far secured tenure-track faculty positions.

From June through August, 25 undergraduates from across the United States, as well as from Canada, China, France, India, Nepal, and the United Kingdom, arrived at CSHL to take part in the historic Undergraduate Research Program. These "URPs" (chosen from among 738 applicants!) had the remarkable opportunity to perform advanced research in the laboratory of a CSHL faculty member. This immersive experience reaped intellectual as well as social rewards for the lucky participants, as in past years. The URP Program, along with the equally innovative and competitive Partners for the Future Program, which brings gifted local high school students to CSHL labs for hands-on research experience, is managed by the Watson School.



Members of the 54th Undergraduate Research Program

Library & Archives

The Institutional Repository is a new on-line resource for publications from CSHL researchers. The repository was initiated this year, with the goal of providing the public with direct access to CSHL discoveries throughout its history. Through this repository, anyone can access these scholarly materials. As an initiative of the Genentech Center for the History of Molecular Biology and Biotechnology at CSHL, Robert Wargas and Mila Pollock examined the history of CSHL's initial involvement in the Biotechnology revolution during the late 1970s/early 1980s, as well as the Lab's continuing relationship with the Biotechnology industry.

The Library hosted The History of Restriction Enzymes October 19-21, 2013. Attended by more than 150 scientists, history scholars, authors, educators, and students, this was



Institutional Repository for CSHL authors

the fifth meeting in the Genentech Center series on the history of science. Herb Boyer, Stu Linn, and Rich Roberts, pioneers in the field of restriction enzymes, were co-organizers, bringing together scientists involved in the discoveries and research on restriction enzymes dating back to the 1950s and covering developments to the present time.

The Archives participated in several events, displaying elements from various CSHL collections:

- Alfred Day Hershey Collection. Materials from the Alfred Day Hershey Collection were displayed at the Scottish Parliament in an exhibit about the philanthropic legacy of Andrew Carnegie, on display from 14 October 2013 until 25 January 2014.
- Extraordinary Women in Science & Medicine. A landmark public exhibition, *Extraordinary Women in Science & Medicine: Four Centuries of Achievement*, held at the prestigious Grolier Club in New York City from September 19 to November 13, 2013, showed materials from the Barbara McClintock Collection, including photos, landmark papers, and a corn cob from the 1960s loaned by CSHL Professor Rob Martienssen.
- From Base Pair to Body Plan: Celebrating 60 years of DNA. A display of more than 200 images related to the Laboratory's history and its science was a central part of the meeting *From Base Pair to Body Plan: Celebrating 60 Years of DNA*, held at CSHL from February 28 to March 3, 2013. This display stayed on exhibit for the entire 2013 meetings season.

CSHL completed the digitization of the archives of James D. Watson and Sydney Brenner, as part of the Wellcome Digital Library Pilot Project "Codebreakers: Makers of Modern Genetics." The result of this multiyear collaborative effort with Churchill Archives Center Cambridge, the University of Glasgow, King's College London, and University College London is free public access to these and other historic collections from an online portal at www .wellcomelibrary.org.

Infrastructure

Woodbury Genome Center Addition

The year 2013 saw the groundbreaking of a 7000-square-foot addition to the Woodbury Genome Center. This expansion of the Genome Center Animal Facility—the Preclinical Experimental



Woodbury Genome Center addition (proposed)



Renovated Cairns building

Therapeutics Facility—will serve as a vital core facility supporting the Laboratory's Cancer Therapeutics Initiative. The facility will house a number of cancer diagnostic and therapeutic resources. Construction is expected to be completed by the end of 2014.

Cairns Laboratory Renovation

The Cairns Laboratory was reconstructed during 2013. The building was originally used as a sheep shed in the early 20th century and was most recently used as a microscopy laboratory. The completion of the new Hershey Building allowed for relocation of microscopy resources and renovation of the Cairns Laboratory. The roof was raised to make way for improved ventilation systems and the building's infrastructure was brought up to modern laboratory standards. The building will be ready for occupancy in 2014 and will house an RNAi Shared Research Resource facility.



Employees at new Syosset Campus

Yellow House Reconstruction: Historic Perspective

The Yellow House was a circa 1830 residence in considerable disrepair. The house had significant foundation and structural issues and had suffered a number of unsympathetic renovations and additions during its lifetime. Deemed uninhabitable, it was demolished and replaced with a new structure.

The Laboratory spent nearly a year working with the State Historic Preservation Officer to obtain permission to demolish and replace the house. Prior to demolition, the Laboratory photographed and documented the entire house, and the records were entered into the Laboratory and New York State archives. A new Yellow House will be used for faculty housing and be ready for occupancy in the spring of 2014.

Syosset Campus

The Laboratory expanded the use of the Syosset Campus in 2013 with the relocation of the Accounting Department from the Nichols Building and the Procurement Department from the Woodbury Genome Center to new offices on the Syosset Campus.

Information Technology

Completed this year was a campus-wide WiFi upgrade that included replacement of aging infrastructure to provide better coverage and speed and greatly improved handling of our high-density venues, notably the Grace auditorium. This project will continue in 2014, providing a further substantial increase in bandwidth.

Information is at the core of our scientific activities. Our ability to collect, manage, and safeguard large volumes of data is critical. Centrally managed CSHL data storage, currently in excess of 3 petabytes, is expected to grow significantly over the coming years. Enterprise-grade data storage of this scale is tremendously expensive to procure and maintain, and the adoption of a financially sustainable data-handling model is essential. To mitigate escalating storage costs, CSHL adopted a new solution, and we are now well positioned to handle current and emerging data storage needs. With the latest expansion, the CSHL system already has a 900-TB disk capacity that can scale up to 21 petabytes.

Additional upgrades were performed to the core and data center distribution layer network for the Hillside and Grace datacenters. Hardware selection was completed, and vendor selection began. To lower maintenance costs and retire aging hardware, we have increased our use of virtual servers.

Community Outreach

CSHL Public Lectures

February 13–Dr. Richard E. Leakey, Professor, Chair, Turkana Basin Institute; Stony Brook University, Department of Anthropology. *Hominid Evolution: How It Has Shaped Human Behavior, Ethics, and Morality.* 2012 Lorraine Grace lectureship on societal issues of biomedical research (rescheduled from 2012 due to Hurricane Sandy).



June 8–Paul A. Offit, M.D., Chief, Section of Infectious Diseases and Director, Vaccine Education Center at Children's Hospital of Philadelphia; Maurice R. Hilleman Professor of Vaccinology, Professor of Pediatrics at University of Pennsylvania School of Medicine. *Alternative Medicine: Sense and Nonsense.* 2013 Lorraine Grace lectureship on societal issues of biomedical research.

June 25–Josh Dubnau, Ph.D., CSHL Associate Professor; Peter Davies, Ph.D., Head and Scientific Director, Litwin-Zucker Research Center for the Study of Alzheimer's Disease and Memory Disorders, Feinstein Institute for Medical Research; Jill Goldman, M.S., M.Phil., Certified Genetic Counselor, The Center for Parkinson's Disease and Other Movement Disorders, Columbia University Medical Center. *Untangling Dementia–Latest Research and Treatments*, cosponsored by CSHL; U.S. Trust–Bank of America; North Shore–LIJ; and St. Johnland Nursing Center.

July 16–Zachary Lippman, Ph.D., CSHL Associate Professor. *Flower Power and the DNA of Feeding the World*, hosted by The Secret Science Club, Brooklyn, New York.

July 17–Kevin J. Mitchell, Ph.D., Associate Professor of Neurogenetics, Trinity College Dublin, Ireland. *The Miswired Brain—How Altered Brain Development Leads to Mental Disorders*.

August 20–Anne Churchland, Ph.D., CSHL Assistant Professor; *Swinging synapses and decision making*, hosted by The Secret Science Club, Brooklyn, NY.

October 7-Rob Martienssen, Ph.D., CSHL Professor. Oil Palm and the Rainforest: Genome Sequencing for Sustainability. Public lecture, Grace Auditorium.

CSHL Public Concerts

April 19:	Ching-Yun Hu, Piano
April 26:	Ying Fang with Ken Noda, Soprano with piano
May 3:	DZ4 with David Kaplan, Woodwind quartet with piano
May 17:	Hye-Jim Kim, Violin (w/piano)
August 23:	Southampton Festival Chamber Orchestra
Sept 12:	Andrew Tyson, Piano
October 4:	Paul Huang, Violin (w/piano)
October 11:	Mikhail Yanovitsky and Galina Sakhnovskaya, Piano and soprano

With help from enthusiastic graduate students and postdoctoral fellows who staff CSHL's public tour program, we conducted 50 campus walking tours throughout the year serving more than 800 visitors. Our guests came from near and wide, including Germany, Italy, and China.

On March 23, more than 400 neighbors came to the main campus for an Open House. Visitors, including many who had never been to CSHL before, plainly enjoyed learning about the spectrum of CSHL research and education programs, as well as ways in which they can be



Open House 2013 (Top left, right, and bottom left)

J. Ipsarro giving a short science talk

involved, as students, friends, and neighbors. During a continuously running series of 5-Minute Science Talks, CSHL postdoctoral researchers engaged audiences throughout the afternoon on topics from "Why haven't we cured cancer?" to "Molecular photography." Videos of these talks are available on YouTube. Free minitours of the campus led by graduate students and Lab postdocs were extremely popular. Kids and adults alike crammed a booth where DNA Learning Center teachers led hands-on biology demonstrations, featuring DNA extraction.

Local families enjoyed the DNA Day Scavenger Hunt while exploring the history of Cold Spring Harbor Village on April 20. Local institutions including the Cold Spring Harbor Library, the Cold Spring Harbor Whaling Museum, the Firehouse Museum, and CSHL's DNA Learning Center took part. DNA Day is celebrated across the country, with educational events sponsored by the National Human Genome Research Institute (NHGRI), a part of the National Institutes of Health. The day commemorates the completion of the Human Genome Project in April 2003 and the discovery of DNA's double helix.

In April, first graders from Goosehill Primary and Friends Academy participated in a science fair. At six stations, they learned about various scientific principles (from chromatography to cell structure to brain anatomy) through hands-on activities and instruction conceived, planned, and led by graduate students and DNALC instructors; 160 students, 14 teachers, and 120 parents participated during the 2 days.

DNALC's Jason Williams led a team of CSHL graduate student and postdoc ambassadors in two iPad app demonstrations at the June 2nd World Science Festival Street Fair in Manhattan's Washington Square Park. CSHL's ambassadors interacted with Festival participants, demonstrating how to use the DNALC-developed apps, 3D Brain, and Gene Screen.

CSHL was pleased to participate in the 10th Long Island 2-Day Walk to Fight Breast Cancer, in which nearly 400 walkers and an equal number of volunteers raised more than \$550,000. Since



Long Island 2-Day Walk

R. Sordella (center right) participated in Swim Across America (SAA)

the Walk started in 2004, CSHL has received more than a quarter of a million dollars for breast cancer research from LI2DAY.

This year, CSHL Associate Professor Raffaella Sordella joined in the Swim Across America (SAA) "Sound to the Cove Swim" at Morgan Park in Glen Cove. Dr. Sordella received \$70,000 from SAA for her research aimed at finding ways to overcome resistance to targeted therapies for non-small-cell lung cancer. Dr. Sordella credited the support she has received from SAA—\$420,000 to date—with providing critical resources to identify a population of cells in lung tumors that are intrinsically resistant to therapy.

CSHL Chief Operating Officer Dill Ayres participated in the October 24 *Long Island Press* "The Future of Healthcare on Long Island" summit that brought research institutions, health care providers, and vendors together to highlight the region's assets and challenges.

A member of the New York Academy of Sciences (NYAS), CSHL was pleased to contribute to an effort to showcase New York's research community. The initiative included the landmark publication of "New York: A Science State of Mind" and a November 18th gala in Manhattan.

CSHL teamed with Research!America, the Society of Neuroscience, Elsevier, and George Washington University to organize the "Research Matters Communications Workshop" for early-career scientists in Washington, D.C. on October 9. The event included a plenary session led by the Alan Alda Center for Communicating Science at Stony Brook University, a panel discussion that included journalists from CNN, Reuters, and NPR, and a session with current and former congressional



Jim and Liz Watson

staff. CSHL Assistant Professors Mikala Egeblad, Alex Krasnitz, and Steve Shea participated as part of the Public Affairs Department's program to help researchers enhance communication with nonscientific audiences.

Looking Forward

2013 marked the anniversaries of two game-changing events for this institution and the world. Sixty years ago, James D. Watson and Francis Crick co-discovered the double helix structure of DNA and set off a revolution in biology and medicine. Fortyfive years ago, Jim and his wife Liz came to Cold Spring Harbor Laboratory, a time when total staff numbered only 100 and the total operating budget was barely \$3 million. With their foresight and leadership what in 1968 was a fledgling research institution became the modern day powerhouse in molecular biology and genetics that is today's Cold Spring Harbor Laboratory.



Dr. James Watson

"Now we are completely different," wrote Jim, looking back on what he had accomplished since taking on the challenge of leading CSHL in 1968. "The science we do, the demanding excellence of our courses and meetings, and the high quality of our publishing program convey to the world outside the aura of a quality postgraduate university. We worry not about becoming good, but instead on how to ensure that we continue to carry out science at the highest possible level" (1977 CSHL Annual Report). We thank Jim and Liz for their continuing dedication to the Laboratory and its continued success. The CSHL family of faculty, students, and employees feted Jim and Liz at a special 1960s-themed picnic on Blackford lawn in summer 2013.

To mark the anniversary of Jim and Francis Crick's DNA discovery and the fact that Jim was invited to CSHL to present the paper for the first time in public at the 1953 Qualitative Biology symposium on viruses, the Meetings & Courses Program organized a special 4-day meeting that began on the discovery's anniversary day of February 28. This meeting was called "From Base Pair to Body Plan" and was organized by Dean Alex Gann, Professor Rob Martienssen, and Meetings & Courses Program Executive Director David Stewart, with guest speakers including Nobel Prize winners Christiane Nüsslein-Volhard, Elizabeth Blackburn, Carol Greider, Craig Mello, and Sir John Gurdon. Celebration of the anniversary included the redecoration of the CSHL bar to look like the famous Cambridge pub, the Eagle, and a gala at Oheka Castle.

Jim and Liz inspired a culture that opened the doors of this institution to participation from the local community and beyond—bringing the intellectual expertise and financial generosity of private philanthropists who have been invaluable to the evolution of CSHL.

The last 60 years at Cold Spring Harbor have yielded great advances in biology. CSHL is now poised for even bigger breakthroughs that will undoubtedly change the world for the better.

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