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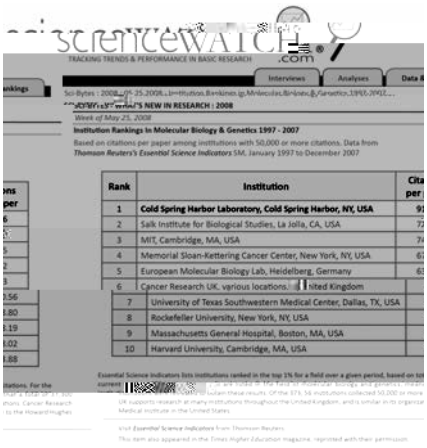
ood scientists know how to udge the relative contributions of their colleagues, peers, and institutions, mostly via a sub ective assessment of research. Indeed, it is part of the process of recruiting new faculty early-career scientists are udged on their potential for an outstanding research career, and Cold Spring Harbor Laboratory CSHL is known as a place in which such young people e cel.

here are, however, some ob ective criteria, such as the number of times research papers are cited by colleagues, indicating on average a relatively high impact.

his year, hompson euters, a science publisher well known for its ssential Science Indicators, again placed CSHL atop a list of 0 heavy hitters in molecular biology and genetics selected from a database comprising more than ,000 research institutions worldwide.

his particular measure of impact, covering the last 10 years, was based on the number of times, on average, papers written by a given institution's faculty were cited by their peers. Other institutions in the top 0 were assachusetts Institute of echnology, Salk Institute for iological Studies, emorial Sloan- ettering Cancer Center, he ockefeller3 niversity, and Harvard3 niversity. Other rating organizations also place CSHL at the very top of research institutions worldwide, and CSHL has consistently been placed as number one in these ratings for the past three decades.



CSHL ranked number one for worldwide impact in molecular biology and genetics

hese ratings are not the only measure of research impact, of course, and we do not use such information when assessing the progress and promotion of our individual scientists. ut in general, the rating does reflect the view I have long held of our institution, based on intimate first-hand knowledge. An e citing research agenda is part of what makes CSHL a great place to work. In 00 , our scientists were as productive as ever, a fact reflected in the highlights of some of the research that appear below.

Mouse Models of Leukemia That Predict Human Response to Chemotherapy

his past year, Scott Lowe and colleagues developed new mouse models for human acute myeloid leukemia A L , a devastating cancer of white blood cells. ost patients with A L receive intense chemotherapy followed by additional chemotherapy cycles or bone marrow transplantation only a uarter of patients are cured and most die within a few months. he range in treatment response is due to A L's genetic heterogeneity, meaning that the 100 or so mutations associated with this form of cancer occur in different combinations in each patient and influence therapeutic outcomes in different ways. Scott's group identified the most commonly occurring mutations in a sample of 111 children with A L and then engineered these mutations into mice, which soon developed leukemia. Of the two most common mutations they observed, one, in an oncogene called *AML1/ETO*, previously had been associated with a favorable therapeutic outcome in people the other, in an oncogene called *MLL,* was associated with an adverse outcome. o design an animal model that predicts these outcomes, the team introduced each mutation individually into stem and progenitor cells along with another oncogene, called ras, which also appears fre uently in human A L and is commonly found in concert with *AML1/ETO* and *MLL* oncogenes. hese altered stem cells were transplanted into mice pretreated with radiation to destroy e isting bone marrow cells. he altered stem cells then took over the host bone marrow and promoted the development of leukemia, which, within weeks, showed the same genetic and pathological features as human A L. ust as in humans, leukemias in mice that received the *AML1/ETO* oncogene were also sensitive to chemotherapy and soon regressed, whereas *MLL*-triggered

S. Lowe

leukemias remained resistant and eventually killed their hosts. hese findings suggest that such models can predict how human cancers will respond to therapy and help to identify genes promoting resistance or sensitivity to any cancer drug. he mouse models also serve as an effective test system for new drugs

R. Martienssen

to the ne t generation. he instructions offered to sperm specifically come in the form of small A molecules that companion cells pass on to sperm. hese small As can inactivate, or ‹silence,› specific A se uences. In this way, they help set up gene e pression patterns in sperm, providing the ne t generation with instructions that specify which regions of the genome should be turned on and which should be switched off and protect the sperm from e pressing genes that might be detrimental when the pollen fertilizes cells for the ne t generation.

A separate study by reg Hannon and colleagues e amined how the germline in fruit flies is protected from genetic parasites called transposons. hese bits of A se uence have infiltrated host genomes over the eons and can cause damage by copying and inserting themselves in random fashion across genomes, disrupting genes and regulatory se uences. o protect themselves from transposons, animal germline cells have developed a molecular immune system, operated by an army of small A molecules called iwi-interacting As pi As and a set of proteins belonging to the iwi family. reg's team discovered that in the ovaries of fruit flies, nongermline, or ‹somatic cells,› that surround germline cells have also developed an antitransposon defense system. Over the years, fruit fly researchers have uncovered genomic mutations that lead to sterility and abnormal development. ecause these defects could have been caused by unchecked transposon activity, mutant flies are a good e perimental resource to uncover e actly how pi A pathways work and how they might get disrupted. Hannon's team analyzed eight such mutants, showing how the genes disrupted in each mutant impact the pi A pathway and how it alters the type and number of pi As that cells are able to generate. hese studies help us understand the broad picture of how the pi A pathway has been genetically stitched together to perform its vital role in protecting the germline and genetic information that will be passed from parents to the ne t generation.

G. Hannon

Mo ile mall R s That et p Leaf Patternin in Plants

Anyone who has taken the time to carefully inspect a plant leaf knows that the top and bottom surfaces are not uite the same. In fact, this difference is the product of a developmental program that establishes an asymmetry crucial for the leaf's function It ensures that the leaf develops a flattened blade optimized for energy production by photosynthesis, with a top surface specialized for light harvesting and a bottom surface containing tiny pores that serve as locales for gas e change. lant scientists have known that the top3bottom a is is established by a signal derived from the meristem, the stem cell-rich growing tip of the plant from which all new leaves arise. Other signals that traffic between the upper and lower sides of the leaf are thought to stably maintain this polar a is. In 00 , ar a immermans and her team were the first group to uncover the identity of one such positional signal a family of mobile small As generated on the upper surface of young leaves but which traffic to form a concentration gradient across each leaf. his graded distribution pattern of small A molecules creates discrete regions of gene activity so that cells in each half of a leaf develop a distinct ‹top› or ‹bottom› identity. esides providing a remarkable e ample of a morphogen-like small A signal, ar a and her team have also shown that the location of the various biochemical ingredients re uired for small A activity can impact pattern formation. ogether, their discoveries e plain how mobile small As can generate leaf patterns during development.

M. Timmermans

dentification of a Protein That nhances Lon -term Memory y Controllin Rest Periods

Students everywhere those who study, at any rate know from e perience that studying improves memory, but only under certain conditions. acts are preserved longer in memory if a student spaces out learning sessions between rest intervals. his past year, i hong and his team discovered how

this so-called ‘spacing effect’ is controlled in the brain at the level of individual molecules.

i has long been interested in genes that when mutated trigger learning and memory disorders such as oonan’s syndrome, a rare genetically inherited disease. ore than half of oonan’s patients have mutations in a gene called *PTP11*, which encodes the SH - phosphatase protein. In contrast to many disease-related mutations that shut off protein production or impair protein activity, these *PTP11* mutations do the opposite they boost the activity levels of SH - phosphatase. o understand how this change impedes long-term memory, hong’s team engineered these mutations into a gene in fruit flies called *corkscrew* that is the functional e uivalent of *PTP11* in humans. he team found that normally, as each learning period ends, SH - phosphatase activity inside stimulated neurons triggers a wave of biochemical signals, which have to peak and decay before the ne t learning session can begin.

hey discovered that the repeated formation and decay of the biochemical signal during each rest interval induces long-term memory. In normal flies, these signal waves took 1 minutes to peak and decay. In the mutants that had e cess protein activity, however, the signaling wave took 0 minutes to decay. his research shows it is crucial that the period of rest should last as long as it takes for a

been associated with -linked mental retardation. Indeed, problems at the synapse in their formation and in the mechanisms through which the strength, or plasticity, of their connections are regulated are thought to contribute to numerous mental and neurological disorders. Linda points out that at least 0 genes have already been implicated in metal retardation. ut what we have not done, to date, is connect the genetic abnormalities to bio-

Likely ri in o acial Cancer ecimatin the Tasmanian e il Population

An international team led by reg Hannon and his former student, lizabeth urchison, of CSHL and the Australian ational3 niversity, succeeded in identifying the likely point of origin for the deadly facial tumors decimating Australia's asmanian devil population Schwann cells, cells of the nervous system which form a tissue type that cushions and protects nerve fibers. he discovery stems from the team's effort to carry out a genetic analysis of tumor cells in devil tumor facial disease.

is a uni ue type of cancer transmitted from animal to animal via biting or other physical contact. umors in the canine-sized devils are mostly found on the face and mouth, but they often spread to internal organs. With no diagnostic tests, treatments, or vaccines currently available, the aggressive disease could wipe out the asmanian devil species, which is found only on that island-state of Australia, in to years. he largest surviving marsupial carnivores, the devils have become a cause c l bre for conservationists worldwide. reg and his team determined the identity of the originating cell by using advanced se uencing technology to uncover the tumors' transcriptome the complete set of genes that are turned on in tumor cells. Comparing this readout to that from other tissues, they found that the tumors' genetic signature best matched that of Schwann cells. Armed with the tumors' genetic profile, researchers now can start hunting for genes and pathways involved in tumor formation. A catalog of devil genes compiled by the Hannon urchison team should be useful in designing vaccines and other therapeutic strategies.

r r r r r B r rus ees

he oard of rustees elected three new members this year ichael . otchan, h. ., oldman rofessor and Chair of the epartment of olecular and Cell iology,3 niversity of California, erkeley, and a former faculty member at CSHL homas uick, resident of irst alm each roperties, Inc., who begins a second period as rustee and Samuel L. Stanley, ., . ., the fifth president of Stony rook3 niversity.

In addition, the oard named ancy arks as an Honorary rustee. ancy served on the board as a rustee from 00 to 00, and participated in the evelopment Committee 00 00 , the Capital Campaign Committee 00 00 , and the uilding Committee 000 00, .

Congratulations to CSHL Scientific rustee Charles L. Sawyers, . ., chair of the Human Oncology and athogenesis rogram at emorial Sloan- ettering Cancer Center, who in September received the 00, Lasker- e akey Clinical edical esearch Award for groundbreaking work on

inner, which alone raised more than million the resident's Council, which raised over ,000 and the Women's artnership for Science luncheon, which raised close to 0,000. he balance was contributed by CSHL Association members.

On behalf of CSHL, our oard of rustees, and our evelopment epartment, I thank all those who helped us achieve our goals. rivate philanthropy is the engine of innovative research, and your contributions are pushing the boundaries of science forward. lease refer to the back of this Annual eport for a complete list of our generous supporters.

ese rc uc e e

Our research and education management teams performed e ceedingly well in the face of the challenges that the world financial crisis presented. CSHL's investigators and administrators worked closely to effectively manage e isting programs under conditions where we had to cut our budget mid year. In an unprecedented team effort, CSHL secured more than million in federal stimulus grants issued under the American ecovery and einvestment Act A A . hese -year funds will support research in cancer, neuroscience, epigenetics, and plant biology, as well as research training and laboratory enhancements.

In applying for research grants, applicants were encouraged to develop innovative and bold ideas in relatively short grant proposals. CSHL scientists had a 0 success rate in securing A A grants, much higher than the national average. I suspect that this is because much of our innovative science is supported by philanthropy or by internal endowment funds, and our scientists are used to proposing bold ideas. If such proposals were submitted in normal individual research grant proposals the so-called O1 mechanism , such ideas would invariably be shot down and not funded. erhaps this is a lesson of how the ational Institutes of Health IH should consider funding some science in the future.

rue to CSHL's legacy as a breeding ground for the latest technologies and approaches to solving biological uestions, CSHL secured special -year grants for transformative research pro ects. Our researchers osh ubnau, h. ., and artha itra, h. ., received these grants for neuroscience pro ects that the IH deemed e ceptionally innovative, high-risk, original, and or unconventional with the potential to create new or challenge e isting scientific paradigms.

We were also encouraged by a pledge of continued support to stem cell research from ew ork overgor neuroscience

themed topics, ranging from the origins of life on a molecular scale to the emergence of species both simple and comple over the last three billion years.

he reputation of CSHL's eetings and Courses rogram continues to grow, as evidenced not only by attendance, which reached a record of 00 this year, but also by e ternal, independent ratings. he September 00 edition of the magazine *Genome Technology* ranked CSHL's iology of enomes meeting as the most recommended among general genomics meetings. Another CSHL meeting called enome Informatics was the most recommended in the ioinformatics Information echnology category.

Cold Spring Harbor Laboratory Conferences Asia convened its first meeting in Suzhou, China in ovember. his invitation-only anbury-style meeting was held in temporary facilities while our purpose-built conference center was being completed. he meeting focused on transgenic crops and served as a prelude to the opening of a complete program of large-scale meetings on a wide range of topics in the biological sciences in 010. he 0-million 00,000-s uare-foot conference center can accommodate up to 00 participants.

he olan A Learning continues to blaze new trails in web-based educational e periences. his year, ALC's io edia roup launched enes to Cognition Online www.g conline.org , which is distinguished by both its content and its presentation on the web. he site uses a uni ue approach to depict the comple and interlocking relationships between different aspects of brain anatomy and function. ust as the brain itself is composed of interconnected networks of cells, the site graphically represents information about these components as members of a vast network, whose nodes are interconnected.

he io edia roup also produced an e citing *iPhone* application that can be download for uick and easy access to a three-dimensional model of the brain and its functions. apidly, this application became one of the top educational tools downloaded to *iPhones*.

he CSHL ress published *Cold Spring Harbor Perspectives in Biology*, a new online publication spanning the complete spectrum of the molecular life sciences. ach issue includes reviews covering a wide variety of topics in molecular, cell, and developmental biology, genetics, neuroscience, immunology, cancer biology, and molecular pathology. Contributions are written by leading researchers in each field and commissioned by a board of eminent academic editors.

r s rs

any of CSHL's younger researchers received prestigious awards this year, recognizing their early-career accomplishments. Adam epecs was made a lingenstein ellow in eurosciences and was also named an Alfred . Sloan esearch ellow. Adam's laboratory is combining its behavioral e pertise with molecular and optical techni ues to monitor and manipulate genetically identified cir-

ach Lippman won a Human rontier Science rogram Career evelopment Award to continue his work in understanding the molecular dynamics that underlie altered developmental fates of certain plant meristems. avel Osten received the c night echnological Innovations in euroscience

budget. Commissioning of the Hillside Laboratory buildings was accomplished, with the new Simons Center for ż uantitative iology and the relocated operations of the CSHL Cancer Center occupying finished space. he Hillside Laboratories comple also contains an additional animal facility that was brought on line in 00. he CSHL Information echnology epartment and an updated and e panded datacenter were relocated to the Hillside comple . his is the new home of the High erformance Computing Center H CC CSHL's very own supercomputer.

or 1 0 years, CSHL has been a proud steward of the Long Island shoreline and local ecosystem.h y gh t g e

In addition to the new construction on the upper campus, we completed scheduled improvements to the ca. 1, elbruck Laboratory building's historic teaching lab space. he pro ect, which was made possible by funds from the Howard Hughes edical Institute, included reconstruction of the top floor and roof of the building and the renovation and e pansion of an e isting conference room.

Across the harbor at the anbury Conference Center in Lloyd Harbor, we also completed the interior renovations to the ca. 1, obertson House, which provides lodging for visiting scientists who attend anbury meetings and participate in CSHL's advanced courses on the latest scientific technologies and techni ues. Installation of modern H AC, electrical, and data systems now make the manor house comfortable for guests throughout the entire year.

he reconstruction and addition to the Carnegie uilding, which is home to the CSHL Library and Archives and he enentech Center for the History of olecular iology, was largely complete by the end of the year. We look forward to the official reopening of the building in the spring of 010.

At the enome Center in nearby Woodbury we constructed a new, state-of-the-art greenhouse to allow for an e pansion of our plant biology program that is being led by a new faculty member, achary Lippman, h. ., who studies varieties of tomato plants to understand the mechanisms that control flower, fruit, and seed production.

o increase operational efficiency across the e panding Laboratory, we are leasing a facility in Syosset that allows us to centralize receiving, storage, and fulfillment operations. his facility also provides needed office and administrative space.

ec e s

G he 1 th Annual avin orden isiting ellow Lecture, in memory of the publisher of *Molecular Biology of the Cell*, was held on arch . he lecture was presented by alph reenspan, Senior ellow in perimental eurobiology, Lewis . and orothy Cullman Senior ellow, he eurosciences Institute, San iego, California.

uring the th Symposium, volution he olecular Landscape, the traditional orcas Cummings emorial Lecture for scientists and guests from the community was delivered by evin adian, rofessor of volutionary iology and aleontology,3 niversity of California, erkeley. he title of the lecture was arwin, over, and Intelligent esign.

On une 1 at eacock oint, at the Lattingtown home of r. and rs. aniel . avison, nearly 1 0 women lunched and learned about the link between viruses and cancer, specifically human papillomavirus H , a prime cause of cervical cancer. he speakers included the ean of the Watson School of iological Sciences and Howard Hughes

Greenhouse at the Woodbury Genome Center

edical Institute Investigator, Leemor oshua- or, h. ., and elicia Callan, . ., obstetrician3gynecologist at the ount Sinai School of edicine3 orth Shore edical roup. oney raised at this event supports women who pursue careers in biomedical research at CSHL.

L. Joshua-Tor

On une 1 , CSHL dedicated the Hillside Laboratories, with remarks from Chairman of the CSHL oard of rustees duardo estre Chancellor meritus im Watson, h. . ill rover, AIA, founding partner of Centerbrook Architects and anners and myself. he keynote address, houghts on the uture of iological Sciences, was delivered by hilip A. Sharp, h. ., obel laureate,3 niversity rofessor, och Institute for Integrative Cancer esearch, assachusetts Institute of echnology.

— CSHL oard Chairman duardo estre and his wife r. illian Shepherd hosted an April 1 reception to announce the theme of the members-only 00 resident's Council program ersonal enomes. Special guests at this anhattan event were Linda Avey and Anne Wo cicki, co-founders of the genome se uencing company and e. he annual fall resident's Council retreat was held on October 1 -1 and featured eter eufeld, co-founder and -director of he Innocence ro ect. Other speakers that weekend included avid otstein, a geneticist and CSHL Scientific rustee sther yson, whose own genome was among the first se uenced in the ersonal enome ro ect laine ardis, Co- irector of he enome Center, Washington3 niversity School of edicine r. hilip arshal of Web Health Services and CSHL Assistant rofessor urinder ickey. Atwal.

— he th ouble Heli edals inner was held at the andarin Oriental Hotel in anhattan on ovember 10. edals for Scientific esearch were presented to Herbert W. oyer, h. . and Stanley . Cohen, . ., who co-discovered recombinant A. Life-long philanthropist and advocate for research athryn W. avis, h. ., was honored for Humanitarianism. In recognition for his unprecedented support of biomedical research, aurice Hank reenberg was presented with the medal for Corporate hilanthropy. iolin virtuoso oshua ell performed with accompaniment by pianist rederic Chiu. he event was cochaired by r. and rs. li road, r. and rs. Christopher avis, s. lorence A. avis, r. and rs. dward . atthews, and r. ichard H. Scheller.

Double Helix Medal

President's Council members Thomas Lehrman, Kristina Perkin Davison, Judy Carmany, and George Carmany (*front row, left to right*) discuss personal genomes

G . — — On ovember , , science ournalist icholas Wade, h. ., presented the first annual lecture, introducing his newly published book, *The Faith Instinct—How Religion Evolved and Why It Endures*.

u c ec ures

— — *The Future of Down Syndrome: Improving Memory and Cognition*—sponsored by the a-

DNALC instructor Ileana Rios at the World Science Festival Street Fair in Manhattan

need. CSHL volunteers prepared and served dinner at the onald c onald house to 0 families of seriously ill children. We also collected 00 pounds of food in support of the Long Island Cares Harry Chapin ood ank.

r r

he financial and economic setbacks in 00 00, will most likely cause a ma or change in the long-term prospects for both philanthropic and federal support of science. We can be secure that our science continues to be world leading and hence will attract support, but increasingly in tight times, we must be aware that both members of Congress and ta payers are increasingly looking at the outcomes of basic research. he economic impact of research is obvious, but changing how we interact with industry is going to be necessary if we are to achieve these goals. ore fundamentally, we must increase the applied value of our research internally. inding a mechanism of funding to do this will create a ma or challenge in the future.

Bruce
President