Highlights of the Year

Research

The year 2012 was another superb one for research at Cold Spring Harbor Laboratory. Here, we provide details of a handful of significant investigations that led during the year to published results in major scientific journals. These are suggestive of the breadth of activity at the Laboratory, as more than 600 scientists and technicians in 52 labs extend our knowledge of cancer cell biology and genetics, as well as cancer treatments; critical circuits and biochemical pathways in the brain that go awry in psychiatric as well as neurodevelopmental and neurodegenerative disorders; and genes and their pathways in plants that will help boost crop yields and extend range. The influence of CSHL faculty publications continues to be extraordinary; once again we were independently rated Number 1 in impact on molecular biology and genetics, worldwide.

The value of the LaboratoryÕs research is gaining broader recognition outside the academic

A Protein That Has a Central Role in Cortical Progenitor Cell Fate

Professor Linda Van Aelst and colleagues have identified a protein key in determining whether cortical progenitor cells will proliferate, make progenitor cells, or differentiate and turn into mature cells. The progenitor cells are known as radial glial cells (RGCs), whereas the mature cells are pyramidal neurons, excitatory nerve cells found in the brainÕs cortex. The protein LindaÕs group shows to be central in regulating RGC proliferation and differentiation is called DOCK7. It previously had been shown by the Van Aelst lab to be highly expressed in the hippocampus and cortex of the developing rodent brain, controlling the formation of axons. Now they show that when DOCK7 is silenced in developing mouse embryos, RGCs remain in their progenitor state, but when overexpressed, RGCs differentiate prematurely. These two processes must be balanced for proper cortical development, and DOCK7 is the key protein in maintaining this balance. The team found that DOCK7 antagonizes the growth of microtubules through an interaction with a protein called TACC3, thus affecting the movement of the nucleus within the cell. This study illuminates a process central to cortical development and may also help further our understanding of abnormal brain development in conditions such as microencephaly, which is characterized by small brain size.

Genome Analyses of Two Major Agricultural Crops Pave Way for Higher Yields

This year, Cold Spring Harbor Laboratory researchers were at the forefront of two ambitious projects to study the complete genomes of two of the so-called big three agricultural crops: maize, better known as corn, and bread wheat. Associate Professor Doreen Ware and colleagues

published results this year that revealed an interesting linkage with genes implicated in Fragile-X syndrome. The most common cause of inherited intellectual disability, Fragile X is also counted among the autism spectrum disorders (ASDs) due to the co-occurrence of autism-like symptoms in some patients. It occurs when a gene called *FMR1* fails to direct nerve cells to manufacture a protein called FMRP. MikeÕs team demonstrated, with help from Ivan Iossifov and other computational biologists at the Laboratory, that ~20% of the genes found to be disturbed in a sample of 343 autistic children appear to be regulated by the FMRP protein. The team Þnds that small de novo mutationsÑas small as a single DNA letter or areas of small insertions or deletions of genetic material up to 15 letters in lengthÑcould be traced in the majority of small children with ASD to the fatherÕs germ cells (sperm) and that their occurrence correlated directly with the fatherÕs age, older dads being more likely to contribute sperm that will result in a child with small autism-related de novo mutations. As Wigler points out, because of research connecting FMRP to

the human *Aβ-42* gene. Other members of YiÕs team, working in a parallel but separate process, also identified EGFR as an AlzheimerÕs drug target, around the same time. That team was testing a library of 2000 synthetic compounds for activity against Aβ-induced memory loss in fruit fly models. Of these, 45 showed positive results after two months of dosing, and three of these, tested in vitro, specifically prevented Aβ42 from activating human EGFR.

Cold Spring Harbor Laboratory Board of Trustees

New York Governor Andrew Cuomo said it best when he visited the campus in October: Ò[For] what it does for the soul, the people it gives hope to, Cold Spring Harbor has always been synonymous with accomplishing the impossible.Ó We do this at all levels of the institution, starting with the Board of Trustees.

Led by Chairman Jamie Nicholls, we are attracting leaders of the highest caliber to our governance bodies. The board welcomed Charles ÒCaseyÓ Cogut, senior corporate partner at Simpson Thacher & Bartlett LLP, with expertise in M&A, private equity, and governance.

Re-elected to the board for an additional 4-year term were Dr. David Botstein, Jacob Goldfield, Leo A. Guthart, Thomas D. Lehrman, Dr. Charles L. Sawyers, Dr. Marilyn H. Simons, Dr. James M. Stone, Paul J. Taubman, and Roy J. Zuckerberg. Officer elections continued the terms of Chairman Nicholls, Vice Chairs Robert D. Lindsay and Marilyn H. Simons, Dr. Leo A. Guthart, Bruce Stillman, Ph.D., and W. Dillaway Ayres. Paul J. Taubman replaced Edward Travaglianti as Secretary.

Many thanks to our friends who are retiring trustees, having served on the board and numerous committees from 2004 to 2012: Stephen Lessing, Andrew Solomon, and Dr. Jerome Swartz.

We mourned the passing of former CSHL trustees Townsend Knight, Robert Van Cleef Lindsay, and John J. Phelan. Rod was one of the founding members of the contemporary Laboratory, serving from 1959 to 1965. Townie served from 1973 to 1995, when he was named Honorary Trustee. John served two terms from 1992 to 1999.

Development

With the help of our board, CSHL capped another year of record-breaking success in fundraising with an Annual Fund total of $6.6 million raised. The 7th Double Helix Medals Dinner Gala raised $3.7 million and honored ParkinsonÕs disease research activist Michael J. Fox, Apple Chairman Art Levinson, and philanthropist Mary Lindsay, who is also a CSHL Honorary Trustee.

this year on the topic of medical ethics. CSHL Director of Research David L. Spector and Associate Professor Lloyd Trotman headed the agenda, which also included DNA Learning Center Executive Director David Micklos. CSHL Trustee Andrew Solomon, acclaimed writer on politics, culture, and society, discussed his new book, *Far from the Tree*. Other guest speakers included Drs. Gilbert Welch of Dartmouth, Jeffrey Berger of Stony Brook University, and Hans Sauer of the Biotech Industry Organization.

Of course, doing the impossible would not even be imaginable without private philanthropic support. In 2012, CSHL was grateful for new major gifts from (in alphabetical order) an anonymous donor, Jamie Nicholls and Fran Biondi, Mr. and Mrs. David Boies, Charitable Lead Annuity Trust under the Will of Louis Feil, Laurie J. Landeau Foundation, Mr. and Mrs. Robert D. Lindsay and Family, the Lustgarten Foundation, the Simons Foundation, and Dr. and Mrs. James M. Stone.

Research Faculty

There is no clearer evidence of our ability to achieve what our Governor called Òthe impossibleÓ than the research accomplishments of our faculty. Many are individually recognized each year by com ohi-hieras gi 7(n)8(d F)24aoatisuudrt Fy. 0.0002 Tc 0.06001 AO 10(u)-1(o)97(s)-16(e)-1((r g)-16

in the Þelds of RNA interference and DNA replication. LeemorÕs laboratory studies the molecular basis of cell regulatory processes, using the tools of structural biology and biochemistry to examine proteins and protein complexes associated with these processes. Her efforts largely center on nucleic acid regulation, including the process of RNA interference and DNA replication initiation

encodes stimuli from the outside world, within and across sensory modalities, to generate specific perceptions that, in turn, trigger complex behaviors. He is interested in how the brain is shaped by sensory experience and what changes occur in neuronal circuits that allow us to learn and remember.

Christopher Hammell was named a Rita Allen Foundation Scholar. As part of the cancer research program, Dr. Hammell is interested in understanding the gene regulatory process that gives rise to normal development in animals as well as alterations in these processes that give rise to diseases such as cancer. Chris also received the special honor of being named the Milton E. Cassel Scholar, a tribute to the memory of a long-time president of the foundation.

CSHL once again teamed up with the National Institutes of Health (NIH) to host a regional conference on funding opportunities and research priorities in the neurosciences. Heading up the agenda were Dr. Thomas Insel, Director of the National Institute of Mental Health; Dr. Robert Finkelstein, Director, Division of Extramural Research at the National Institute of Neurological Disorders and Stroke (NINDS), and Dr. Alan L. Willard, Deputy Director of NINDS. Supported by the Alfred P. Sloan Foundation and organized by the CSHL Office of Sponsored Programs, CSHL faculty members Florin Albeanu, Anne Churchland, and Steve Shea facilitated the discussions with faculty from Columbia, SUNY Stony Brook, New York University, and the Massachusetts Institute of Technology (MIT).

The laboratories of CSHL's 52 principal investigators are supported by an active community of postdoctoral fellows, this year numbering nearly 160. The Postdoc Liaison Committee was created to give the postdoctoral community a formal organization through which to pursue its own agenda of enhancing the postdoctoral education experience at CSHL. Headed by an elected group of six, they are the primary organizers of the twice-yearly postdoctoral collaboration and

less affluent parts of the world. We were saddened to hear that Dr. Murray passed away before this Annual Report went to print.

In August, WSBS opened its doors to the 14th incoming class of nine students: Nitin Singh Chouhan, William Donovan, Talitha Forcier, Yu-Jui (Ray) Ho, Irene Liao, Paul Masset, Annabel Romero Hernandez, and Abram Santana. These new degree candidates come to us from the United States, France, India, Mexico, and Taiwan.

The WSBS now counts 54 Ph.D. graduates who are thriving in the Òoutside world.Ó They continue to publish in top journals and secure prestigious independent positions, fellowships, and awards. Eleven of our graduates have secured tenure-track faculty positions, and, as such, they are now receiving federal grants and publishing papers as independent researchers.

Current students continue to win prestigious fellowships and prizes. In 2012, Colleen Carlston was selected into the National Science FoundationÕs East Asia and Pacific Summer Institutes for U.S. Program. In addition, she received a National Science Foundation Graduate Research Fellowship. John Sheppard also was awarded a National Science Foundation Graduate Research Fellowship and received a National Defense Science & Engineering Graduate Fellowship from the Department of Defense. Melanie Eckersley-Maslin was awarded a Keystone Symposium Travel Fellowship. She was also awarded an American Society for Cell Biology Travel Fellowship to attend the annual conference. WSBS students have published more than 210 papers to date, many in the most prestigious journals.

The National Institutes of HealthÕs National Institute for General Medical Studies renewed the SchoolÕs Training Grant for a period of 5 years. Despite very tight funding, the NIH recognized the outstanding achievements of the program, the students, and the faculty in the funding of this award. The training grant funds six students and also serves as an endorsement of the SchoolÕs excellence.

The annual Gavin Borden Visiting Fellow Lecture ÒElectron transfer in times of stress: New roles for redox active antibiotics,Ó was presented on April 23 by Dianne K. Newman, Ph.D., Professor of Geobiology and Howard Hughes Medical Institute Investigator at the California Institute of Technology.

Twenty-six undergraduates (selected from 884 applicants, the largest pool to date) from around the United States as well Canada, Switzerland, Ireland, and the United Kingdom formed the 53rd cohort of the Undergraduate Research Program (URP). This yearÕs URP Faculty Directors were Anne Churchland and Michael Schatz. The historic 10-week program for undergraduate students convenes in the summer, and it provides some of the Þnest college students a priceless opportunity to conduct sophisticated research at the side of a CSHL investigator.

Under the direction of Professor David Jackson, the Partners for the Future Program for high school seniors attracts the best and brightest aspiring scientists to an average of about a dozen of our labs each year. Established by Dr. James Watson in 1990, the program provides an opportunity for gifted Long Island high school students to have hands-on experience in biomedical research.

In August, Leemor Joshua-Tor stepped down as Dean of the WSBS after 5 years of outstanding leadership. As the third leader of a school known as one of the nationÕs most innovative Ph.D.-granting programs, Leemor advanced the curriculum in signiÞ

research at the Laboratory, studying the molecular basis of cell regulatory processes using the tools of structural biology and biochemistry.

The year saw the introduction of two new meetings, *Regulatory and Noncoding RNAs* and *Epigenetics and Chromatin*, which drew strong attendance and featured a high proportion of unpublished research. We anticipate these meetings will each become regular biennial series. Two exist,

within a high-technology suburb (SIP). The scientific program includes large symposia and meetings, training workshops and Banbury-style discussion meetings. CSHA is a wholly owned subsidiary of CSHL and is not beholden to outside partners in terms of our scientific programming. The 50% growth in meeting attendance between the second and third year of operations bodes well for the future.

Banbury Center

In its 35th year of operations, Banbury Center continued to have an active role in the LaboratoryÕs educational mission. At the beginning of the year, the Conference Room underwent a major renovation. By autumn, it was the turn of Sammis Hall, which had gone largely untouched since its opening in 1981. These efforts ensure that participants in our programs have the fully modern and up-to-date accommodations that they expect.

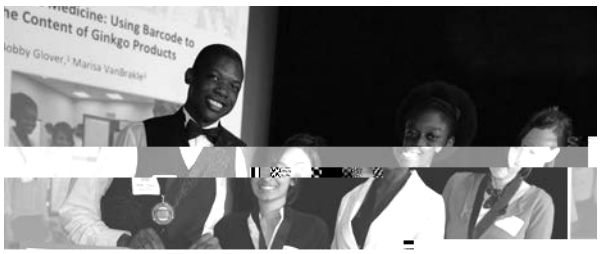
Despite the renovation work, BanburyÕs facilities were used intensively throughout the year, hosting 18 meetings as well as six lecture courses and two Watson School courses. CSHL postdocs came on two occasions for a retreat and the Robertson family came for their annual meeting. As usual, CSHL is happy to help our neighbors; this year, the Cold Spring Harbor School District board twice used the Banbury Center facilities.

We welcomed back the Boehringer Ingelheim Foundation, which, for several years, has brought its fellows for training in writing papers and giving talks. The National Institute for Mental Health returned for its Brain Camp, providing the brightest clinical fellows to high-level neuroscientists, encouraging them to think of taking up research. For the second year, Carl Cohen of Science Management Associates taught a ÒLeadership in BioscienceÓ workshop.

Banbury CenterÕs first meeting on patenting was held 30 years ago, just 2 years after the 1980 *Chakrabarty* case (which declared that a modified microbe was patentable). In 2012, the question of patents was brought into sharp focus by the recent Myriad Genetics case involving patents covering the *BRCA* genes. The meeting, *Patenting Genes: New Developments, New Questions*, discussed this and other unresolved issues.

DNA Learning Center

DNA Learning Center (DNALC) Executive Director David Micklos received the 2012 Elizabeth W. Jones Award for Excellence in Education from the Genetics Society of America. David was recognized for bringing Òthe excitement of DNA science into the educational curriculum for thousands of students, high school teachers, and undergraduate faculty.Ó



Urban Barcode Project grand prize winners

On June 6, nine finalist teams of high school students representing eight public high schools, plus home schooling, from all of the five boroughs of New York City, presented their submissions to the first-ever NYC Urban Barcode Project competition. They were selected from more than 200 students on 75 teams, whose research posters were judged by conservation and genetic biologists and education experts. For most students, it was their first independent research project. Twenty-six percent of contestants were African American or Latino, groups that are underrepresented in science.

New York City institutions, including the American Museum of Natural History, Genspace, New York Botanical Garden, Brooklyn Bridge Park, and the

Rockefeller University, partnered with the DNALC to provide facilities and mentoring to the student teams. Developed and executed by the DNALC with funding from the Alfred P. Sloan Foundation, the Urban Barcode Project was the large-scale attempt to use barcoding projects

gene regulation, replication, checkpoints and DNA repair, RNA function and control, development, stem cells, and diseases such as cancer, representing the broad scope of science covered by the journal.

In its second year of sales, the review journal *Cold Spring Harbor Perspectives in Biology* continues to increase notably in revenue and usage. The concept of a "new type of review journal" with subject collections that build monthly has been well received, as has its consistent editorial excellence. It received its first impact factor this year. The newest review journal, *Cold Spring Harbor Perspectives in Medicine*, completed its first year of publication with exceptional usage of collections about HIV, Alzheimer's, Parkinson's, and addiction.

New print books and new e-books included *Genome Science*, a new and long-awaited collection of laboratory exercises by the teaching staff at the DNA Learning Center. In June, a new edition of the laboratory manual *Molecular Cloning* was published. Long established as the gold standard for molecular biology techniques, and by far the most successful book ever published by the Press, with more than 200,000 copies sold, this new edition was a complete revision by authors Joe Sambrook and Michael Green, assisted by a dozen expert contributors. A classic of a different sort also reappeared, co-published by the Press and Simon & Schuster: James Watson's 1968 autobiographical account of the discovery of the structure of DNA, *The Double Helix*, which was named during the year as one of the Library of Congress's 88 "Books that Shaped America." CSHL Professors Alex Gann and Jan Witkowski illustrated and annotated the text with footnotes,

Receiving building

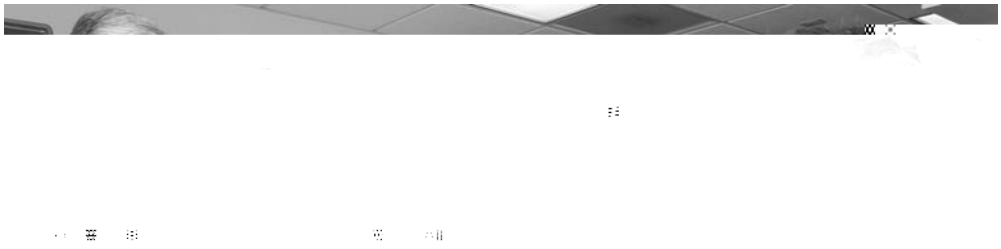
Hershey building

Hillside laboratory of Professor David Tuveson, one of our latest recruits and a distinguished pancreatic cancer researcher who is also the Deputy Director of CSHLÕs Cancer Center.

Drs. Tuveson and Stillman briefed the dignitaries on CSHLÕs new Cancer Therapeutics Initiative, which New York State is helping to fund by seeding the construction of a new Advanced Drug Testing Facility located at the Woodbury Genome Center. The central idea in our Cancer Therapeutic Initiative is to create a translational pipeline that will enable us to help develop a new generation of cancer drugs that will be more effective and less toxic than those currently in use. Another objective is to significantly reduce the time it takes to identify and test candidate drugs, to accelerate their path to the clinic.

Stuart Rabinowitz, President of Hofstra University, and Kevin Law, President and CEO of the Long Island Association, both co-chairs of the Long Island Regional Economic Development Council, highlighted the importance of public support for cutting-edge science in driving economic development of the region and in providing new high-quality jobs. The GovernorÕs next stop that day was the Broad Hollow Bioscience Park, an incubator facility that CSHL helped to found and where CSHL spin-off biotech companies have made their start.

CSHL is pleased to join with Brookhaven National Laboratory, SUNY Stony Brook, Hofstra University, and North Shore LIJ in Accelerate Long Island, an initiative to expand on the success of the Broad Hollow Science Park and strengthen the bioscience economy of Long Island.



Governor Cuomo (*center*) tours Hillside Laboratory

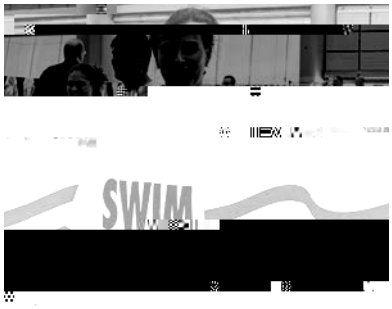
The GovernorÕs visit came just a month after the visit of Lieutenant Governor Duffy, who chairs the stateÕs regional economic development councils. ÒThis is a great intersection of public health and economic development,Ó said Mr. Duffy of CSHL. ÒThis is a jewel in New York State and to see the brain power and expertise we have here makes us all very proud.Ó

As I have already mentioned in brief, thanks to well-laid preparation plans and hard workÑnot to mention some luck associated with the outgoing tideÑthe Lab was able to ride out Hurricane Sandy at the end of October. By moving equipment and data storage to higher ground, bringing up elevators, sandbagging, and using diesel-powered backup generators for electricity, all essential scientific operations continued through the storm and in its aftermath. Even attendees of the Nuclear Receptors and Disease meeting continued undaunted, producing a decent slogan that attendees and the Lab community will long remember: ÒScience vs. Sandy. . .Science Wins!Ó

Our preparedness allowed us to help our neighbors. We were in constant contact with the leadership of Laurel Hollow village, firefighters, police, friends, and residents, who benefited from our food services, WiFi access, and warm spaces. CSHL even hosted TV coverage of the 2012 Presidential Election in Grace Auditorium, for CSHL families as well as community residents who were still without power more than a week after the storm.

A special thank you to those on our campus who helped us all weather the storm, in particular:

stories we deliver. The CSHL blog, Labdish, grew too, and we now host guest bloggers who represent the CSHL campus community from grad students to professors. Thanks, Michael Schatz, Anne Churchland, Clare Rebbeck, Antoine Molaro. Hats off to CSHL faculty who are active in social media, promoting their own ideas and providing perspectives on the latest developments in biology and genetics.



R. Sordella

CSHL Public Lectures

A. Mills

CSHL Public Concerts