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101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120 121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140 141 142 143 144 145 146 147 148 149 150

## Cancer

Liver cancer is the fifth most frequent neoplasm worldwide. However, owing to the lack of effective treatment options, it is the third leading cause of cancer deaths. By generating and for testing new treatments.

To gain a better understanding of the molecular causes of liver cancer, the researchers x.366 1, 26 0 Tc (cIAP1)Tj /T12 1 Tf -0.0001 Tc 0.nT/

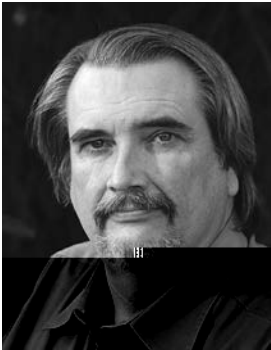
tions— now collectively as “aneuploidy”—arise in two principal ways: as a consequence of abnormal cell division or as a result of cell fusion. In both cases, aneuploid cells have an abnormal genetic makeup (e.g., too few or too many copies of a particular chromosome or chromosome segment) and they frequently die, but not always.

Researchers have long known that cancer cells—very much alive—are often aneuploid. Whether aneuploidy is a cause or a consequence of a cancerous state is still being debated. But in any case, given that cell fusion causes aneuploidy and that aneuploidy may cause cancer, it follows that cell fusion may cause cancer. This is why “innocuous” viral infections come in.

Domini and Yuri first observed that cultured human cells are fused through the action of a particular virus (Vason-Pfizer monkey virus [MPV], one among many “fusogenic” viruses). As expected, the resulting hybrid cells are aneuploid and fail to grow. However, the researchers next showed that if one of the cell fusion partners is engineered to carry a particular mutation in an oncogene or a tumor suppressor gene, then a significant number of the resulting hybrid cells grow and are thus potentially cancerous. Yuri’s group is currently exploring whether such proliferating fused cells are produced by viral infections in animal models. If they are, then the work of sorting out which of the many known fusogenic viruses might contribute to human cancer will likely begin in many laboratories.

## Genetics and Biotechnology

Rice feeds more than half of the world’s human population. Estimates indicate that the rice crop yields will have to be increased by about 30% over the next two decades to meet a projected increase in demand.



W.R. McCombie

W. Richard Combs, his CSHL colleagues, and other members of the 10-nation International Rice Genome Sequencing Project have reported a highly accurate, “finished” DNA sequence of the entire rice genome. The complete rice genome sequence—which reveals some 33,000 genes on the 12 chromosomes of rice—provides the raw material for many studies aimed at improving the agricultural yields of the world’s most important food source. Moreover, because the rice genome is closely related to that of other major cereal grasses (including corn, wheat, barley, rye, sorghum, and millet), the complete rice genome sequence is an extraordinarily useful resource for identifying genes of interest in a group of crop plants that collectively supply two thirds of humanity’s food supply.

The study reveals thousands of genetic markers in the rice genome that are of immediate use to plant breeders and others working to improve rice agriculture. It also generates the first finished genome sequence of any crop plant, making rice a powerful model for how to use genome sequence information to improve many other aspects of agriculture. The finished rice genome sequence builds upon draft sequences previously published by the private companies Monsanto and Syngenta. As such, it is an excellent example of a successful public-private partnership that saves the public consortium both time and money.

Enabling scientists to identify genes that underlie agriculturally important traits, a draft of the rice genome sequence released by the public consortium in 2002 has already spurred both biotechnological and conventional plant-breeding approaches to increasing rice yields. The new, finished rice genome sequence has the potential to accelerate those efforts. The availability of the sequence should greatly speed the hunt for genes that increase yield, protect against diseases and pests, and improve other traits of rice and several other cereal crops.

Although most people probably do not give too much thought to leaves, they are in fact crucial light-harvesting and gas-exchanging organs, without which agriculture as we know it, not to mention life on Earth itself, would be very different.

To the naked eye, the top and bottom surfaces of leaves look rather similar. Closer inspection reveals that they are highly specialized regions that arise through a complex series of molecular events. Marja Timmermans has recently made a number of important discoveries concerning these events and how they instruct unspecialized stem cells to form the specialized top (light-harvesting) and bottom (gas-exchanging) surfaces of leaves.



M. Timmermans

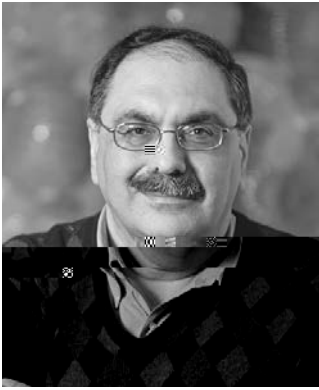
One of Marja's projects explores the role of a gene called *GL1* in plant development. Corn plants with a normal *GL1* gene develop broad, flat leaves with distinct top and bottom surfaces, as usual. In contrast, mutant plants lacking a functional *GL1* gene develop long, thin leaves that are "all bottom, no top." This means that the *GL1* gene is somehow required to specify the formation of top surfaces of leaves. To find out how, in parallel with other experiments (see below), Marja and her colleagues, including postdoctoral fellow Fabio Nogueira, isolated the *GL1* gene. They discovered that *GL1* is similar to another gene with a known role in generating biologically powerful snippets of RNA called "targeting small interfering RNAs" (ta-siRNAs). This is cluster #1, which specifies "top" by promoting ta-siRNA formation. Cluster #2 came from examining a different sort of small regulatory RNA called "microRNA166" (miR166). Marja's group has previously shown that in normal plants, miR166 is present in the cells that generate the bottom surfaces of leaves but is absent from adjacent cells that generate the top surfaces of leaves. In short, miR166 means "bottom."

If ta-siRNAs mean "top" and miR166 means "bottom," then what might ta-siRNAs and miR166 mean to each other? Does one control the other? Marja and her colleagues answered this question by determining whether the pattern of miR166 expression is altered in plants (mutants) that lack ta-siRNAs. The result (cluster #3 and a major discovery): In the absence of ta-siRNAs, miR166 is present both in its usual "bottom" cells in the cells that normally generate the top surfaces of leaves. This is consistent with the idea that in normal plants, ta-siRNA activity blocks miR166 expression in the "top" cells. It also explains why the leaves of mutants are "all bottom, no top." In such mutants, the "bottom promoting" activity of miR166 is abnormally present in the "top" cells and transforms the fate of those cells from top to bottom.

Through the work of other scientists, including some of CSHL's own (e.g. Hannon, Limor Joshua-Tor, Rob Martienssen), small RNAs akin to miR166 and ta-siRNAs have recently been shown to have important roles in the biology of many organisms, including humans. Therefore, the discovery by Marja and her colleagues that the opposing activity of two small RNAs can control major developmental events in plants establishes a paradigm that is likely to have broad implications for the biological and biomedical sciences.

Neuroscience

CSHL neuroscientist Igori (Irisa) Eni Iolopov and his colleagues have identified which cell type among several different kinds of neural precursor cells in the brain is the sole target of the widely prescribed antidepressant Prozac. This discovery might enable a new generation



G. Enikolopov

of more specific treatments for depression, with fewer side effects, to be developed. It also lays the foundation for many studies of the factors that control how, when, and where new neurons are generated from stem cells in the brain. Such work could eventually lead to cell replacement therapies for neurodegenerative and other brain disorders including Alzheimer's and Parkinson's disease.

It has been known for some years that Prozac (fluoxetine) is likely to relieve the symptoms of depression by somehow causing more neurons to be present in a particular region of the brain (the "substantia nigra"). But the origins of these neurons, and how Prozac promotes their existence, have been a mystery. Until now, by profiling the full set of markers produced by different kinds of cells in the brains of adult mice, Grisha's group—supported by postdoctoral fellow Juan Manuel Encinas—first defined discrete steps in the

complex process, called neurogenesis, that converts unspecialized stem cells into mature, specialized neurons.

Next, knowing that Prozac treatment somehow increases the number of neurons in the brain, the researchers tested which step in the neurogenesis pathway might be stimulated by Prozac. They found that Prozac treatment specifically stimulates the generation of a kind of cells they dub "amplifying neural progenitors" or ANPs—the second step in the neurogenesis pathway from stem cells to mature neurons.

To address the controversy surrounding the use of Prozac in children and in pregnant women, Grisha's group is currently testing the effects of the drug on brain neurogenesis in juvenile and pregnant mice. The results of those experiments should provide valuable information for assessing the possible effects of Prozac and related drugs on fetal and adolescent brain development. The researchers are also using the tools they have developed to explore whether other treatments for depression, including other drugs and deep brain stimulation, act in the same way as Prozac or in different ways. In addition, they are screening for new drugs that stimulate ANP cells to multiply and thus expand the production of brain neurons for the treatment of neurodegenerative diseases.



Z. Mainen

It is a classic upper-middle-class dilemma: Should we buy a perfect second home in an area that takes hours to get to or should we settle for something closer but not as nice? In the real world, an equivalent decision-making situation might be, "Was the food I liked better down this alley or over there?"

By discovering that particular rat brain neurons combine or "integrate" dissimilar pieces of information (e.g., location vs. reward), Zach Mainen and his colleagues have begun to learn how the brain controls decision-making and goal-oriented behaviors. Examples of these include foraging and navigation in animals and in humans, whether to buy a particular second home or, generally, whether to favor a long-term benefit over immediate gratification.

Zach's recent study represents the first time that brain neurons have been shown to integrate spatial and reward information. Its results contrast with a previous "purely economic" view that neurons in the orbitofrontal cortex (OFC) are involved solely in assessing value. Moreover, the study has implications for understanding pathological states in humans that affect decision-making, motivation, and emotions such as addiction, depression, obsessive-compulsive disorder, autism, and other disorders of thought or mood.

The research was supported by graduate student Claudia Furst, who recorded the activity of OFC neurons while rats performed an odor discrimination task that they had previously learned to accomplish. In the task, the animal receives a test odor ("A" or "B") by po-

ing its nose into a centrally located odor port. Next, the animal chooses odor A or odor B as being the same as the test odor by putting its nose into a choice port located to its right (odor A) or left (odor B). If the animal chooses correctly, it receives a reward (a drop of water). As expected, many of the OFC neurons actively signal "I'm getting a reward" when the animal moves right or left, i.e., toward odor A or odor B. Surprisingly, however, several of the neurons signal "I'm getting the reward to my right," whereas several others signal "I'm getting the reward to my left."

One of Zach's next steps will be to examine what happens in the brain while the animals are first learning to recognize new odors. Through this work, the researchers hope to gain a greater understanding of learning and memory as well as the neural basis of perception, motivation, decision-making, and other aspects of behavior.

#### MEMBERSHIP AND BOARD OF TRUSTEES

The Board of Trustees was pleased this year to welcome four new members: John C. Phelan, Managing Partner and cofounder of MSD Capital, L.P.; Jamie C. Nicholls, recently a General Partner and currently a Limited Partner at Forstman Little & Co.; Donald Everett Axinn, writer, investor and publisher in the New York area, and committed public servant; and Landon Clay, Managing Member of East Hill Management Company.

Concluding their terms as Trustees this year were Arthur M. Spiro and Susan Lynn Lindquist. Mr. Spiro was first elected to the Board in November 1999, and was then re-elected to a second term in 2002. He was active on several committees, including Audit, Executive, and Woodbury Economic Research Center, and he served for 6 years as the Chairman of the Dolan DNA Learning Center Committee. Dr. Lindquist was elected to the Board in 2002 and brought her expertise to bear on the Tenure and Appointments Committee throughout her term.

We said a sad goodbye to Winoy Van der Poel Russell, Honorary Trustee, who passed away in March, 2006. Mrs. Russell was an active member of the Board of Trustees since 1984, serving as Secretary from 1985 to 1987 and from 1992 to 1997. A legendary fundraiser, her pet project at the Laboratory was the Dolan DNA Learning Center, and she was instrumental in the establishment of its Corporate Advisory Board.

The Cold Spring Harbor Laboratory Association (CSHLA) raised a total of \$1,155,000 this year under the leadership of Association president Joe Donohue. We say than s to Mr. Donohue who serves his second term as president in 2006, going double duty while also serving as a Trustee of the Board. New Directors in 2006 include Joe Amalia, Suzanni DiMaio, Nancy Esparr, Larry Gillman, M.D., and Scott J. Ratner, M.D.

#### CONSTRUCTION AND FACILITIES

The Hillside Campus Construction Dedication Ceremony on October 15 marks the transition from constructing the infrastructure for new facilities to construction of the facilities themselves. Much of the work done this year has been groundwork for the construction of six

- The L'Esprit and Jean Quic Building
- The Donald Everett Axinn Building
- The Winnet Family Building

The bright, crisp afternoon of the ceremony brought dozens of well-wishers, including CSHL faculty, staff, dignitaries, and most importantly the honorees and their families whose names will grace these facilities. Once complete, the Laboratory's research space will increase by nearly 40%.

The festive day included a solemn note with fond memories of Jean Quic who passed away earlier this year after naming the L'Esprit and Jean Quic Building for Cancer Research after his late husband and CSHL Trustee L'Esprit C. Quic, Jr. Long-time residents of Laurel Hollow and neighbors of the Laboratory, their legacy at CSHL lives on through their gifts and the continuing involvement of the family.

In planning for the Hillside Campus, CSHL has worked to be environmentally and aesthetically sensitive to the unique environment of Cole Spring Harbor. The new facilities have been designed to encourage efficiency and easy communication between buildings and scientists. Together, they will function as an academic village at the southern end of the campus, stylistically within the broader village of science that now exists.

Much of the infrastructure work completed this year consisted of ensuring adequate storm water drainage for the previously wooded site. Rather than employ the conventional approach of installing an enormous quantity of dry walls to accommodate storm water, our civil engineers adopted an ingenious approach. They designed water quality rain gardens and bio-retention ponds to collect and treat storm water runoff before it enters the harbor. This approach not only provides an environmentally sound means of treating storm water, but also creates additional naturalized water features on the campus, adding beauty and a wildlife habitat.



Hillside Campus Dedication Ceremony

## News & Events

Rob Martienssen was elected a Fellow of the Royal Society, distinguished for fundamental discoveries on the epigenetic mechanisms that regulate transposon silencing, gene control, and stem cell function in plants. He was also named by the Royal Society as a major contributor to sequencing the genome of *Arabidopsis thaliana*, the first plant genome sequence completed. This is one of the highest honors that can be accorded a scientist, and CSHL now adds Martienssen to its list of previously elected Fellows: Jim Watson, Nic Tsonis, and myself.

The Leukemia & Lymphoma Society elected Bill Tansley as one of five researchers to receive its prestigious Stohllman Scholar Award, recognizing his outstanding contributions to the advancement of blood cancer research. The focus of his work is a protein, Myc, known to contribute to the growth of leukemia and lymphoma cancer cells.

Sandra J. Kuhlman and Elinor Rial each received the National Alliance for Research on Schizophrenia and Depression Young Investigator Award. Sandra is studying in an animal model the role of EA Argic synapses in the prefrontal cortex have in memory impairment in people with schizophrenia. Elinor is working on glutamate receptor trafficking and synaptic plasticity, since glutamate abnormalities have been implicated in psychotic disorders.

CSHL Fellow Ira Hall received a 2006 Burroughs Wellcome Fund Career Award in the Molecular Sciences. This award provides early-career biomedical researchers with funding over a 5-year period to foster their development and help them make the critical transition to independent investigators. Ira is using DNA microarray technology to explore DNA copy-number fluctuations and epigenetic inheritance in the mouse, an important model system for many diseases including cancer.

Thomson-ISI added the CSHL Press journal *Genetics* to its "Top 10 Scientific Journals in All Areas" list for the second time, 1995-2005. Edited by Terri Grodzic for, this journal presents research papers of broad general interest and biological significance in molecular biology, molecular genetics, and related fields. Thomson-ISI provides a service that measures the impact of some 7 million papers published in 11,000+ journals in 22 major scientific fields.

—a comprehensive, user-friendly Web guide to cancer biology created by the Molecular Group of CSHL's Dolan DNA Learning Center—was selected as an official "Site of the Day" by About Systems Incorporated, joining the ranks of other winners that include NIH, Cancer, and Family Motors.

A publication by Limor Joshua-Tor and her colleagues Niraj Tolia, Fabiola Rivas, and Greg Hannon was selected as the "New Hot Paper" by Thomson Scientific's Essential Science Indicators. "Purified Argonaut2 and an siRNA form recombinant human RISC" won this distinction by virtue of it being cited more frequently than 10% of all other studies in numerous journals surveys.

CSHL was selected to be part of a consortium that will benefit from a \$100 million grant from the Starr Foundation. CSHL, The Broad Institute of MIT and Harvard, Memorial Sloan-Kettering Cancer Center, The Rockefeller University, and Weill Cornell Medical College will collaborate on research aimed at understanding cancer at its most fundamental levels and at developing new approaches to the prevention, diagnosis, and treatment of many forms of the disease.



R. Martienssen





We gratefully acknowledge support of \$100,000 or more from Mr. and Mrs. Lanon T. Clay, Mr. and Mrs. Norris Darrell, The Shelby Cullom Davis Foundation, The Coleman Fung Foundation, Jeff Hawkins and Janet Strauss, Jamie Nicholls and Fran Lionoi, The Robertson Foundation, Dr. and Mrs. James Stone, and The Roy J. Zuckerman Family Foundation.

## **B a C a c R e a c h S e**

The Laboratory greatly appreciates the many supporters of our breast cancer research program. This includes several local grassroots groups that provide not only much needed funds, but also public awareness and outreach. This year, we were fortunate to receive support from Breast Cancer Awareness Day in memory of Elizabeth McFarlane, Breast Cancer HELP, Erin Covert-Carrs, The Breast Cancer Research Foundation, the Cold Spring Harbor Main Street Association, Fine Arts Today (F.A.C.T.), Mr. and Mrs. Richard Corson, Long Island 2-Day Walk, Long Islanders Against Breast Cancer (L.I.A.C.), the Manhasset Women's Coalition Against Breast Cancer, the Peter and Pam Omieyar Fund, the Judi Shresh Memorial Foundation, the Waldbaum Foundation, the West Islip Breast Cancer Coalition for Long Island, the Women's Insurance Network of Long Island, and the Char Channell/WALK for Women Breast Cancer Fund.

## **C o n s t r u c t i o n**

This year 2006 was a busy one for the Facilities Department, with multiple simultaneous construction projects being undertaken in addition to the work on the Hillside Campus.

The James Laboratory renovation—a multi-year project in which nearly the entire building has been reconstructed to meet modern needs—continued from 2005, with only one laboratory and two offices remaining to be completed in 2007. The replacement of the Grace Auditorium bluestone patio, begun in the fall of the previous year, was completed in time for the meeting and course season, and the ground-water-cooled chiller plant that was to service the Grace and Harris buildings was completed, meeting the increased cooling demands with greater efficiency. This also paved the way for the complete renovation of the Harris building mechanical systems, which, when completed in 2007, will increase the building's capacity by more than 40%. Additionally, the Domestic building chiller, running above its design capacity and beyond its useful life, was replaced with a new unit of increased capacity and far greater efficiency.

2006 also saw a continuation of the Laboratory's program to upgrade and improve its residential properties. The final Hooper apartment, the remaining two Firhouse apartments, and the Ross cottage were all renovated during this year. Additionally, the car-ta-ber quarters of the Robertson House—previously composed of two cramped rooms—were expanded and renovated into a comfortable apartment for the live-in car-ta-ber.

Other small projects include those in support of meetings, courses, and special events. Restrooms in Grace were enlarged to accommodate the increased size of meetings. Power and lighting were improved in the Rush Auditorium, and offices were constructed in MacLeod Hall to accommodate the increased size of the events planning staff.

Less visible, but usually as important, several key infrastructure projects were completed as well. Several sections of the Laboratory's underground high-voltage power mains were replaced. Underground fiber optic network cables were extended to areas not previously serviced. And the Laboratory's water main was extended both to accommodate future expansion into the Upper Campus and to connect to residential properties at the north end of the campus, which were previously fed by well water. Two highly visible infrastructure projects are the curbing and stabilizing of the Davnport lawn parking lot and a major drainage project intended to divert the stream running through the campus around the foundations of the Domestic Laboratory during 100-year floods, two of which occurred within a single month the previous year.

**Symposium**

**Symposium**

The 71st Symposium—"Regulatory RNAs"—once again included the annual Dorcas Cummings Lecture. Ron Pastan's outstanding lecture on "The Emerging World of Small RNAs" was presented to a mixed audience of scientists and lay friends and neighbors of the Laboratory. Following the lecture, more than 20 of our neighbors graciously opened their homes and hosted dinner parties for Symposium participants and Laboratory friends alike.

**Gavin Brown Visiting Fellow**

The 12th Annual Gavin Brown Visiting Fellow Lecture—in memory of the publisher of *Development*—was held on Tuesday, May 1. Dr. Michael Levin, Professor of Molecular and Cellular Biology at the University of California, Berkeley, presented the lecture entitled "Genetic Networks for Fly Gastrulation and Heart Formation in Sea Squirts."

**David Clark 100th Anniversary**

On August 26 and 27, the Laboratory commemorated the centennial of the birth of Max Delbrück (September 4, 1906). Delbrück, who frequently visited during the 1940s through the 1960s, was a scientific leader who conducted his research and began Cold Spring Harbor Laboratory's Phage Course. With Salvador Luria and Alfred Hershey, he founded the "Phage Group" to research bacteriophages (viruses that attack bacteria) in

## PUBLIC

The CSHL Cultural Series is a tradition in which an eclectic mix of artists, writers, and scientists present lectures, concerts, and exhibits that provide compelling glimpses of how we experience, discover, live in, and make sense of our world. Open to the public, the aim of the Cultural Series is to stimulate, inspire, and entertain.

### 1

Simon Baron-Cohen, Professor of Developmental Psychopathology at University of Cambridge and Director of the Autism Research Centre in Cambridge.

### 2

Scott Lowy, HHMI Investigator/Professor, Cold Spring Harbor Laboratory.

### 1

Ilana Pennberg, Adjunct Associate Professor, Francis University Research Associate, Harvard University Lecturer, The Alex Foundation.

2  
Rui Shi and Chris Gaudi, piano and oboe

2  
Martin Kasi, piano

Asmira Woodward-Pag, violin

20  
Ivanov, piano

2  
Julia Albers, cello

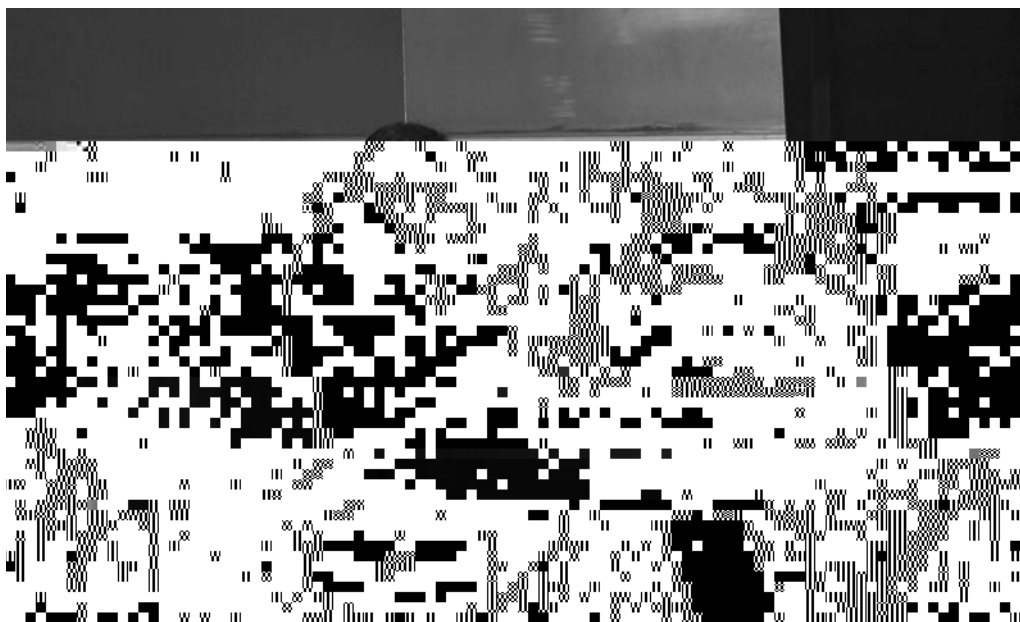
2  
Orion Weiss, piano

1  
Eraltaçgil, cello

0  
Wonny Song, piano



O. Weiss



W. Song

1  
Thomas Miglioranza, baritone

1  
Daniel Phillips, violin

2  
Jupiter String Quartet

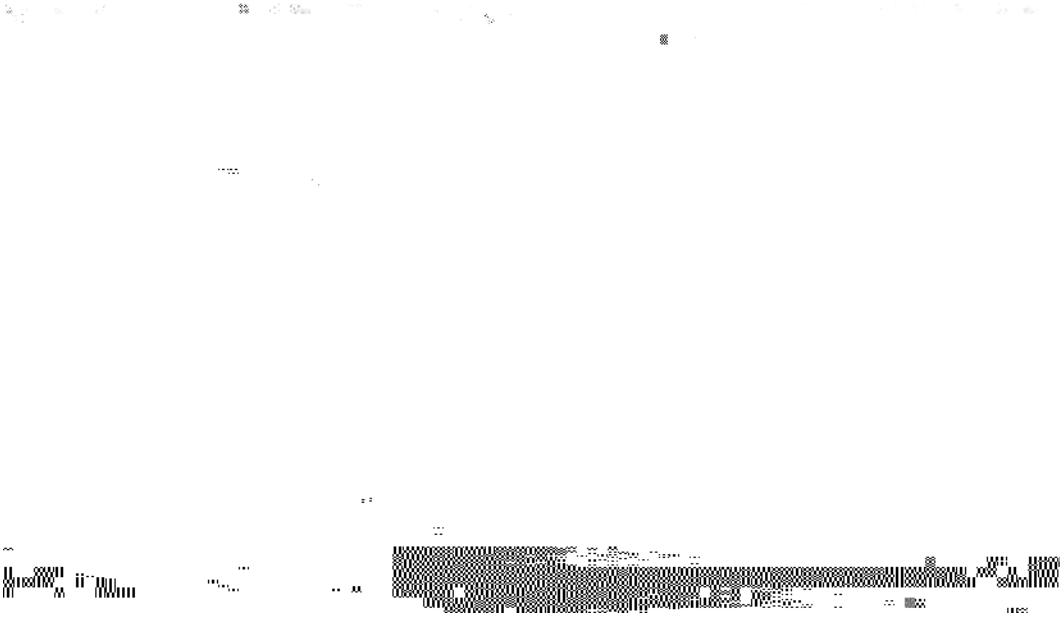
***E n b.***

The 2005 Photographer-in-Residence Ryan Kinzler exhibited his works in Rush Auditorium throughout the month of July. The photographs of many CSHL researchers were captured during his residency the previous summer.

Paul Liam Harrison, Artist and Printmaker, exhibited his work in a show entitled "Pertaining to Origins," held in the Racine Room of Macfarlane Hall from September 26 through October 1.

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Hillside Campus expansion

**Community Outreach**

Cole Spring Harbor Laboratory participated in a number of community outreach events, including the sixth annual Pancreatic Cancer Walk at Old Westbury Gardens, the Long Island 2-Day Walk to Fight Breast Cancer, the Long Island Prom, outdoor the Long Island Car's Food Drive, and numerous activities to support the Ronald McDonald House at Schriner Children's Hospital in New Hyde Park.

**Year in Review**

The year 2006 was one that propelled Cole Spring Harbor Laboratory forward. The foundations for the future were firmly set this year. Structurally, we moved mountains to set the cornerstone for the Hillside Campus expansion whose buildings will proudly bear the names of some of our most generous supporters. We celebrated the history and legacy of our Long Island campus with yet another successful symposium and numerous other concerts and lectures. The Double Helix Medal begins a new legacy that receives national recognition for CSHL's dedication to raising awareness about the importance of genetics research for improving the health of people everywhere. The year 2006 should inspire us all to continue to move forward and realize the full potential of this institution. Thanks to our Trustees, our faculty and staff, and to our supporters for making this possible.

