Ca c

Liv r canc r is th fifth most f u nt n oplasm worl wi . How v r, owing to th lac of ff ctiv tr atm nt options, it is th thir l a ing caus s of canc r aths. y g n rating

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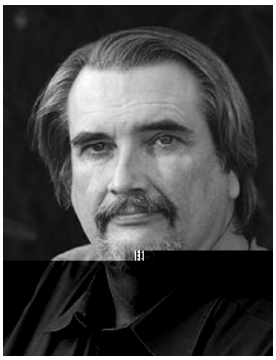
tions— nown collectively as “aneuploidy’—arise in two principal ways· as a consequence of abnormal cell division or as a result of cell fusion. In both cases, aneuploid cells have an abnormal genetic ma up (e.g., too few or too many copies of a particular chromosome or chromosome segment) and they frequently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

Researchers have long nown 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. ut 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 where “innocuous’ viral infections come in.

Domini and Yuri first observed that cultured human cells are fused through the action of a particular virus (Sendai virus, Jason-Pfizer mon ey virus [JPV], 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 wor of sorting out which of the many nown fusogenic viruses might contribute to human cancer will li ely begin in many laboratories.

Green Biotechnology

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



W.R. McCombie

W. Richard McCombie, 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 32,000 genes on the 12 chromosomes of rice—provides the raw material for many studies aimed at improving the agricultural yield 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 revealed 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 generated 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 drafts sequences previously published by the private companies Monsanto and Syngenta. As such, it is an excellent example of a successful public-private partnership that saved the public consortium both time and money.

ynabling 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.

Pa M c a G c

Although most p opl probably do not giv too much thought to l avs, th y ar in fact crucial light-harv sting and gas-exchang organs, without which agricultur as w now it, not to m ntion lif on Earth itself, would b v y diff r nt.

To the na ked y, the top and bottom surfac s of l avs loo rather similar. Closer insp ction r vals that th y ar highly sp cializ d r gions that aris through a compl x s ri s of mol cular v nts. Marja Timm rmans has r c ntly mad a numb r of important discov ri s conc rning th s v nts and how th y instruct unsp cializ d st m c lls to form th sp cializ d top (light-harv sting) and bottom (gas-exchanging) surfac s of l avs.

M. Timmermans

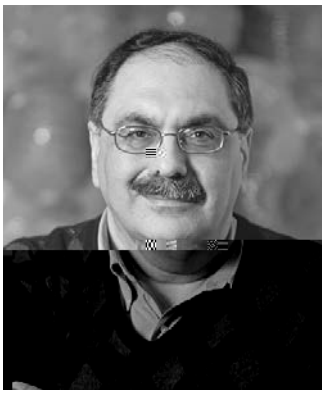
On of Marja's proj cts xplor s th rol of a g n call d in plant d v lopm nt. Corn plants with a normal g n d v lop broad, flat l avs with distinct top and bottom surfac s, as usual. In contrast, mutant plants lac ing a functional g n d v lop long, thr ad-li l avs that ar "all bottom, no top." This m ans that th g n is som how r quir d to sp cify th formation of top surfac s of l avs. To find out how, in parall l with oth r xp rim nts (s b low), Marja and h r coll agu s, including postdoctoral f llow Fabio Nogu ira, isolat d th g n. Th y discov r d that is similar to anoth r g n with a known rol in g n rating biologically pow rful snipp ts of RNA call d "trans-acting small int rf ring RNAs" (ta-siRNAs). This is clu #1, i.., sp cifi s "top" by promoting ta-siRNA formation. Clu #2 cam from xamining a diff r nt sort of small r gulatory RNA call d "microRNA166" (miR166). Marja's group had previously shown that in normal plants, miR166 is pr s nt in th c lls that g n rat th bottom surfac s of l avs but is abs nt from adjac nt c lls that g n rat th top surfac s of l avs. In short, miR166 m ans "bottom."

If ta-siRNAs m an "top" and miR166 m ans "bottom," th n what might ta-siRNAs and miR166 m an to ach oth r Do s on control th oth r Marja and h r coll agu s answ r d this u stion by d t rmining wh th r th patt rn of miR166 xpr ssion is alt r d in plants (mutants) that lac ta-siRNAs. Th sult (clu #3 and a major dis-cov ry). In th abs nc of ta-siRNAs, miR166 is pr s nt both in its usual "bottom" c lls in th c lls that normally g n rat th top surfac s of l avs. This is consist nt with th id a that in normal plants, ta-siRNA activity bloc s miR166 xpr ssion in th "top" c lls. It also xplains why th l avs of mutants ar "all bottom, no top." In such mutants, th "bottom promoting" activity of miR166 is abnormally pr s nt in th "top" c lls and transforms th fat of thos c lls from top to bottom.

Through th wor of oth r sci ntists, including som of CSHL's own (Gr g Hannon, L mor Joshua-Tor, Rob Martienssen), small RNAs a in to miR166 and ta-siRNAs hav r c ntly b n shown to hav important rol s in th biology of many organisms, including humans. Th r fo , th discov ry by Marja and h r coll agu s that th opposing activity of two small RNAs can control major d v lopm ntal v nts in plants stablish s a paradigm that is li ly to hav broad implications for th biological and biom dical sci nc s.

N f c c

CSHL n urosci ntist Grigori (Grisha) Eni olopov and his coll agu s hav id ntifi d which c ll typ among s v ral diff r nt in s of n ural pr cursor c lls in th brain is th sol targ t of th wid ly pr scrib d anti-pr ssant Prozac. This discov ry might n ab a n w g n ration



G. Enikolopov

of mor 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 "dentate gyrus"). But the origins of these neurons, and how Prozac promotes their existence, have been a mystery. Until now. By profiling the cellular markers proteins produced by different kinds of cells in the brains of adult mice, Grisha's group—spearheaded 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 dubbed "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 recent world, an equivalent decision-making situation might be, "Was the food I like 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, in general, 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 spearheaded by graduate student Claudia Feierstein, 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 nos into a centrally locate odor port. Next, the animal chooses odor A or odor as being the same as the first odor by po ing its nos into a choice port located to its right (odor A) or left (odor). If the animal chooses correctly, it receives a reward (a drop of water). As expected, many of the OFC neurons actively signaled "I'm getting a reward' when the animal moved right or left, i.e., toward odor A or odor . Surprisingly, however, several of the neurons signaled "I'm getting the reward to my right,' whereas several others signaled "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 wor , the researchers hope to gain a greater understanding of learning and memory as well as the neural basis of perception, motivation, decision-ma ing, and other aspects of behavior.

[illegible]

The oard of Trustees was pleased this year to welcome four new members: John C. Phelan, Managing Partner and cofounder of SD Capital, L.P. Jamie C. Nicholls, recently a General Partner and currently a Limited Partner at Forstman Little & Co. Donald Everett Axinn, writer, respected investor and builder in the New Yor 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 Lee Linsquist. Mr. Spiro was first elected to the oard in November 1 , and was then reelected to a second term in 2002. He was active on several committees, including Audit, Executive, and Woodbury Economics Research Center, and he served for 6 years as the Chairman of the Dolan DNA Learning Center Committee. Dr. Linsquist was elected to the oard in 2002 and brought her expertise to bear on the Tenure and Appointments Committee throughout her term.

We said a sad goodbye to Wendy Vander Poel Russell, Honorary Trustee, who passed away in March, 2006. Mrs. Russell was an active member of the oard of Trustees since 1 84, serving as Secretary from 1 85 to 1 87 and from 1 , 2 to 1 , 7. 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 oard.

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. Donahue who served his second term as president in 2006, doing double duty while also serving as a Trustee of the oard. New Directors in 2006 included Joe Amelia, Suzanne Diamaio, Nancy Esparr, Larry Gellman, M.D., and Scott J. Ratner, M.D.

[illegible]

The Hillside Campus Cornerstone Dedication Ceremony on October 15 marked the transition from constructing the infrastructure for new facilities to construction of the facilities themselves. Much of the wor done this year has been groundwor for the construction of six

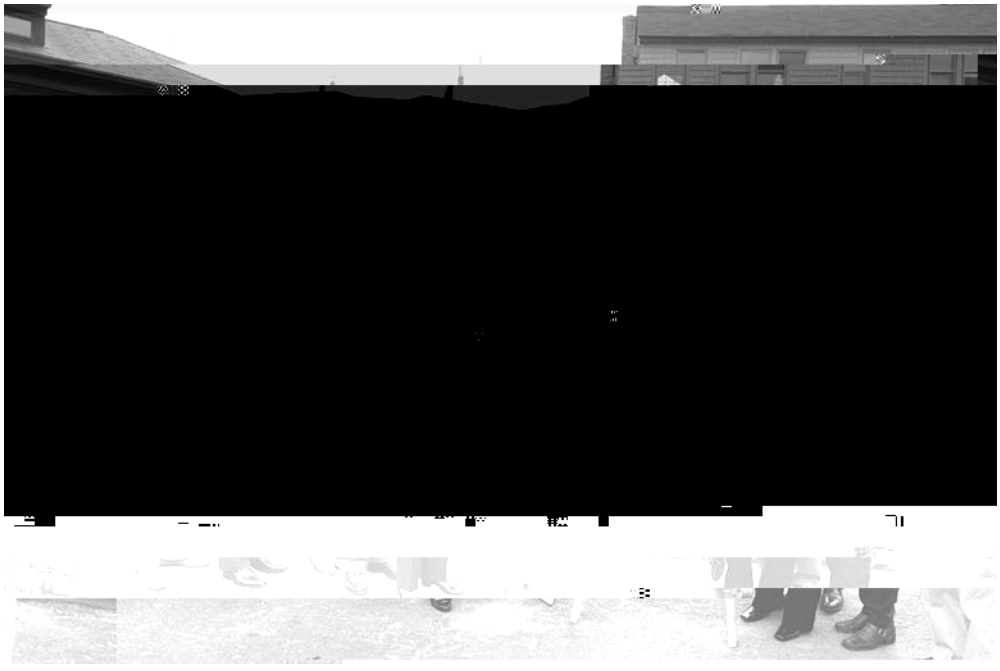
- The Leslie and Jean Quic uilding
- The Donald Everett Axinn uilding
- The Wynnet Family uilding

The bright, crisp afternoon of the ceremony brought dozens of well-wishers, including CSHL faculty, staff, dignitaries, and most importantly the donors 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 Leslie and Jean Quic uilding for Cancer Research after her late husband and CSHL Trustee Leslie 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 continued involvement of the family.

In planning for the Hillside Campus, CSHL has worked to be environmentally and aesthetically sensitive to the unique environment of Cold 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.

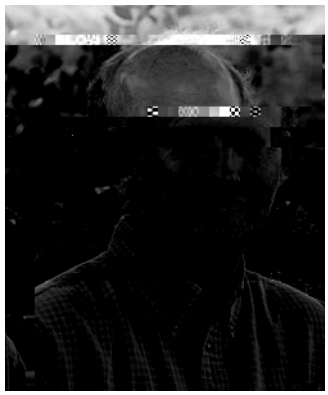
Much of the infrastructure work completed this year consisted of ensuring adequate storm water drainage for the previously wooded site. Rather than employ the conventional approach of installing an enormous quantity of dry wells to accommodate storm water, our civil engineers adopted an ingenious approach. They designed water quality rain gardens and bioretention 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

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 noted by the Royal Society as a major contributor to sequencing the genome of , 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 Ton s, and myself.

The Leukemia & Lymphoma Society selected ill Tansey 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 wor is a protein, yc, nown to contribute to the growth of leu emia and lymphoma cancer cells.



R. Martienssen

Sandra J. Kuhlman and Elenore Real each received the National Alliance for Research on Schizophrenia and Depression Young Investigator Award. Sandra is studying in an animal model the role GA Aergic synapses in the prefrontal cortex have in memory impairment in people with schizophrenia. Elenore 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 urroughs Wellcome Fund Career Award in the iomedical Sciences. This award provides early-career biomedical researchers with funding over a 5-year period to foster their development and help them ma e 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 & to its "Top 10 Scientific Journals in All Areas" list for the ecade 1 , 5–2005. Edited by Terri Grodzic er, this journal presents research papers of broad general interest and biological signficance 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 io edia roup of CSHL's Dolan DNA Learning Center—was selected as an official "Site of the Day" by Adobe Systems Incorporated, joining the ran s of other winners that included Ni e, Cartier, and ntley otors.

A publication by Lecturer 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 Argonaute2 and an siRNA form recombinant human RISC" won this distinction by virtue of it being cited more frequently than , , % of all other studies in numerous journals surveyed.

CSHL was selected to be part of a consortium that will benefit from a $100 million grant from the Starr Foundation. CSHL, The road Institute of IT and Harvard, emorial Sloan-Kettering Cancer Center, The Rockefeller University, and Weill Cornell edical 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.

We gratefully acknowledge support of $100,000 or more from Mr. and Mrs. Landon T. Clay, Mr. and Mrs. Norris Darrell, The Shirley Cullom Davis Foundation, The Coleman Fung Foundation, Jeff Hawkins and Janet Strauss, James Nicholls and Francesca Rosenfeld, The Robertson Foundation, Dr. and Mrs. James Stone, and The Roy J. Zuckerberg Family Foundation.

Breast Cancer Research Support

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 McFarland, Breast Cancer HELP, Green Cove Cares, The Breast Cancer Research Foundation, the Cold Spring Harbor Main Street Association, Find A Cure Today (F.A.C.T.), Mr. and Mrs. Richard Gordon, Long Island 2-Day Walk, Long Islanders Against Breast Cancer (L.I.A.B.C.), the Manhasset Women's Coalition Against Breast Cancer, the Perry and Pam Omidyar Fund, the Judi Shush Memorial Foundation, the Waldbaum Foundation, the West Islip Breast Cancer Coalition for Long Island, the Women's Insurance Network of Long Island, and the Clear Channel/WALK for Women Breast Cancer Fund.

[illegible]

The 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 multiyear 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 groundwater-cooled chiller plant that was to service the Grace and Harris Buildings was completed, meeting the increased cooling demand 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 Demerec 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 Firehouse apartments, and the Ross cottage were all renovated during this year. Additionally, the carriage quarters of the Robertson House—previously composed of two cramped rooms—were expanded and renovated into a comfortable apartment for the live-in caretaker.

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 Bush Auditorium, and offices were constructed in Blackford Hall to accommodate the increased size of the events planning staff.

Less visible, but equally 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 Davenport lawn parking lot and a major drainage project intended to divert the stream running through the campus around the foundations of the Demerec Laboratory during 100-year floods, two of which occurred within a single month the previous year.

S [illegible]

The 71st Symposium—"Regulatory RNAs"—once again included the annual Dorcas Cummings Lecture. Ron Pasternak'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.

Ga[illegible] B[illegible] V[illegible] F[illegible]

The 12th Annual Gavin [illegible]orden Visiting Fellow Lecture—in memory of the publisher of [illegible]—was held on Tuesday, May [illegible]. Dr. Michael Levine, Professor of Molecular and Cell [illegible]iology at the University of California, Berkeley, presented the lecture entitled "Gene Networks for Fly Gastrulation and Heart Formation in Sea Squirts."

D[illegible]b[illegible] ck 100[illegible] B[illegible]n[illegible] a C[illegible]b a[illegible]

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 brilliant research and helped found Cold Spring Harbor Laboratory's Phage Course. With Salvador Luria and Alfred Hershey, he founded the "Phage Group" to research bacteriophage (viruses that attack bacteria) in

Public Lectures

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 aron-Cohen, Professor of Developmental Psychopathology at University of Cambridge and Director of the Austism Research Centre in Cambridge.

2

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

1

Irene Pepperberg, Adjunct Associate Professor, randeis University Research Associate, Harvard University Leader, The Alex Foundation.

2
Rui Shi and Chris Gauci, piano and oboe

2
Martin Kasi , piano

Asmira Woodward-Page, violin

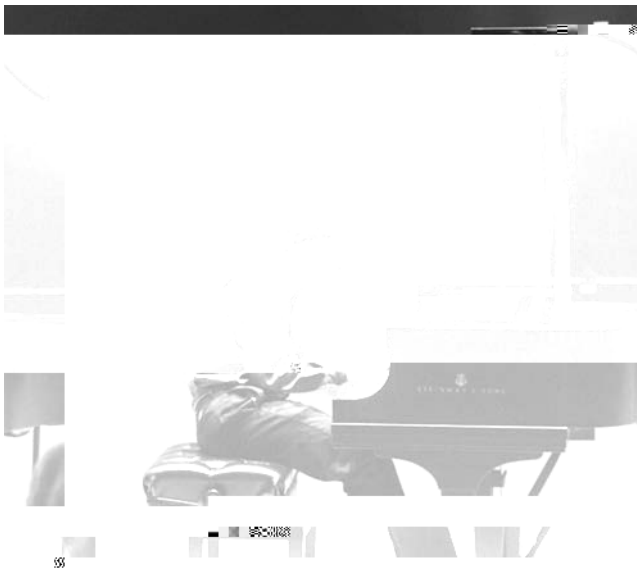
20
Gleb Ivanov, piano

2
Julia Albers, cello

2
Orion Weiss, piano

1
Efe altacigil, cello

0
Wonny Song, piano



O. Weiss

W. Song

1
Thomas Meglioranza, baritone

1
Daniel Phillips, violin

2
Jupiter String Quartet

E nb.

The 2005 Photographer-in-Residence Ryan Lanz exhibited his work 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 Racker Room of Blackford Hall from September 26 through October 1.

Hillside Campus expansion

Community Outreach

Cold Spring Harbor Laboratory participates 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 Promenade, the Long Island Cares Food Drive and numerous activities to support the Ronald McDonald House at Schneider Children's Hospital in New Hyde Park.

Message from the Director

The year 2006 was one that propelled Cold 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 received 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.