COLD SPRING HARBOR LABORATORY
Volume 31 • Issue 2 • 2011

HARBOR TRANSCRIPT

Turning Biological Discovery into Cancer Therapy

PRESIDENT'S MESSAGE

I am optimistic that the powerful approach Cold Spring Harbor Laboratory is taking in cancer research will contribute to turning currently fatal cancers into manageable, survivable chronic illnesses, or even better, true cures. CSHL's cancer research program began under Jim Watson's leadership in 1968 and I have been directing our Cancer Center since 1992. Our last four decades brim with research and technology breakthroughs — some of which are highlighted in this magazine. On the eve of the 125th anniversary of CSHL's founding, we are poised to pursue a new initiative to develop better cancer drugs faster.

CSHL's new Cancer Therapeutics Initiative (CTI) has foundations in one of our historic strengths, genetic analysis. It applies our genome analysis capabilities in human tumors to identify genetically defined subsets of each tumor type. RNA interference (RNAi) technologies developed here can rapidly sort through these subsets to identify the Achilles' heel of cancers and suggest new therapeutic targets, essentially linking therapy to the underlying genetics of a tumor. Validating these targets in mouse models of human cancers perfected by CSHL scientists should increase the success rate of drugs that eventually enter into the clinic.

We have learned the hard way — through many failed cancer drugs — that there is no substitute for defining the molecular mechanisms of the disease in its many forms and understanding the cellular response to therapies within the living environment in which actual tumors form, grow and spread.

What we are proposing in the CTI will work best if scientists in industry and academia can interact seamlessly. Academic scientists lack the resources to develop drugs for testing in the clinic. But given well-validated targets, industry has proven to be very effective at running the large-scale clinical trials to demonstrate efficacy. The problem is that industry has not been good at discovering targets with a high probability of clinical success. This is where I expect academia can play a major role.

While the CTI is a new opportunity, CSHL will continue vigorously to pursue basic research on small RNAs, genome structure and organization, cellular signaling pathways, cell proliferation, gene regulation and other aspects of fundamental biology which will lead us to new technical capabilities and discoveries we cannot predict. Combining our outstanding basic research with an institutional desire to discover new cancer therapies will ensure that CSHL remains at the forefront of science and medicine.

Harbor Transcript

Volume 31, Issue 2, 2011

Harbor Transcript is published by the Department of Public Affairs of Cold Spring Harbor Laboratory. For additional copies or more information, please contact:

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Courtesy Huroki Taniguchi, Z. Josh Huang: 1, 8–9;
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Courtesy Matthew Camiolo/ Sordella Lab: 2;
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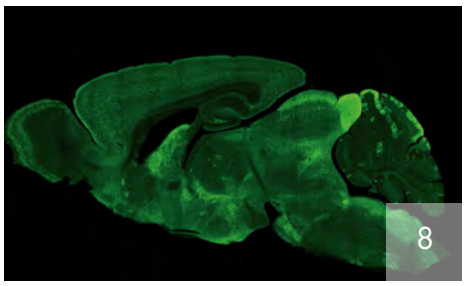
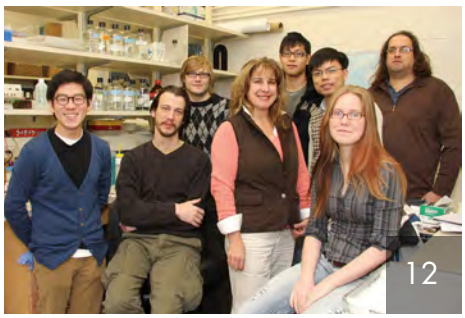
Grad student Matt Camiolo studies lung cancer cells in the Sordella lab.



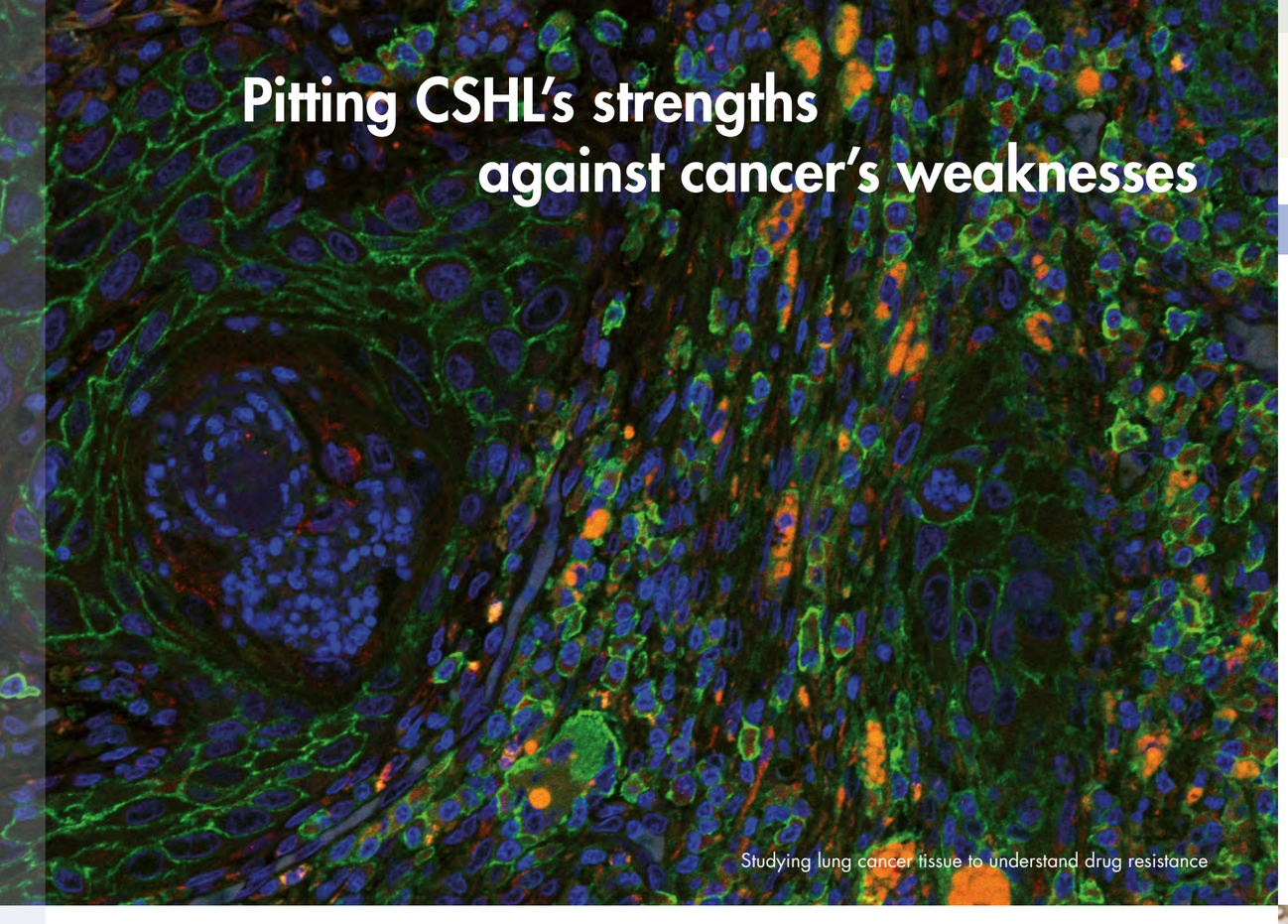


FEATURES

FACULTY & FRIENDS

On the cover:
Graduate student Shipra Das and Postdoc Ken Sahashi in Prof. Adrian Krainer's lab are among the many investigators at CSHL who are developing fresh conceptual approaches and new technologies to treat cancer.

Pitting CSHL's strengths against cancer's weaknesses



Studying lung cancer tissue to understand drug resistance

Cancer research is making a pivotal turn. At Cold Spring Harbor Laboratory, new ways of analyzing the vulnerabilities of cancer cells, new knowledge about the mechanisms of drug resistance, and new approaches to discovering therapeutic targets and rapidly testing their effectiveness *in vivo* are vitally enhancing our ability to confront the disease. Here, on Laboratory grounds, where so many consequential cancer discoveries have been made since James D. Watson made the illness a primary focus of the scientific program in 1968, the "war" on cancer now enters a potentially climactic stage.

The great strengths of CSHL's cancer program, built up steadily over the years, are being integrated with innovative technologies and approaches in President Bruce Stillman's new Cancer Therapeutics Initiative. The Initiative aims to rapidly identify novel therapeutic targets and validate them in mouse models that closely mimic the behavior of specific human cancers. In addition to offering insights into cancer's molecular mechanisms, the preclinical testing of drug candidates within living animals — an important aspect of the Initiative — allows researchers to evaluate cancer's response to new therapies and glean information that can be used to modify treatment strategies and increase the number of drugs that enter the clinic, and, it is hoped, the rate at which they succeed.

A leader in cancer research for four decades, CSHL has been a National Cancer Institute-designated cancer research center since 1987. Now at a point of unprecedented technological and intellectual maturity, the Laboratory's cancer program is playing a leading role in transforming cancer treatment from its long "hit-or-miss" phase that relied on toxic chemotherapies and radiation treatments that kill cells indiscriminately, causing massive and often fatal side effects, to a new stage likely to be characterized by ensembles of targeted therapies tailored to reflect genomic and epigenetic complexities of individual tumors. We sample below only a fraction of the research efforts under way in the laboratories of CSHL principal investigators to address major cancer types: breast, prostate, ovarian, cervical, leukemia, lymphoma, melanoma, lung, liver, brain and pancreatic.

BREAST CANCER:

Battling on multiple fronts

One in eight American women will develop breast cancer and about 90% of those diagnosed will survive at least five years. Several CSHL research groups are working to improve these odds by developing technologies to better define individual risk for this cancer; to detect it at early stages, when it is most treatable; to find out more about its basic causes and cellular origins; and to use genomic data to guide and improve its treatment.

Knowing whether an individual is susceptible to breast cancer is the first step toward saving a life. CSHL quantitative biologists led by Mickey Atwal are developing algorithms — computer-driven mathematical procedures — that hunt for genetic variants that increase breast cancer risk. These methods previously helped link genetic variations in two human genes, the cancer-causing *MDM4* and the tumor suppressor *TSC1*, to increased risk for breast cancer among Northern European and Ashkenazi Jewish women. The team's current search is within a genetic network controlled by the powerful tumor suppressor gene *p53*, which is mutated in more than 50% of all cancer patients.

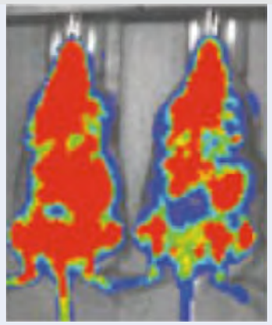
In an effort to provide breast cancer patients and doctors with actionable information that can direct treatment decisions and reduce the risks inherent in a trial-and-error approach to therapy, CSHL scientists led by Michael Wigler and Jim Hicks have developed a "DNA biopsy." This is a diagnostic test that aims to distinguish between cancers that are likely to spread and therefore should receive aggressive treatment, and cancers that are benign and therefore should not be treated. As normal breast cells develop into tumor cells, they accumulate chromosomal rearrangements — structural alterations to DNA that increase or decrease the copy numbers of genes. (Most human cells should have two copies of each gene — one inherited from each parent.) To date, the CSHL team has analyzed copy-number changes in over 1,000 patients and identified three distinct DNA profiles associated with different outcomes. Their new diagnostic test, which is included in clinical trials being carried out at Yale Medical Center and Memorial Sloan-Kettering Cancer Center, should yield critical information about which patients are most likely to benefit from treatment with specific drugs.

The team has also developed another powerful technique, one that can identify dangerous tumor cells from very small samples (such as those obtained via fine-needle biopsy) based on chromosome rearrangement patterns. Called single nucleus sequencing (SNS), this technique reveals the order in which genetic changes occur as tumors develop. Such mutational patterns are now being analyzed to identify changes that signal impending metastasis and to find markers that can predict which breast cancers will respond to specific therapies. Wigler, Hicks and colleagues are now trying to make SNS less costly and scale it up to profile the genomes of thousands of cells at the same time. Such an advance will make it feasible for SNS to be used as a monitoring tool for the first signs of cancer by looking for cancer cells in blood and learning more from biopsies to increase treatment efficiency.

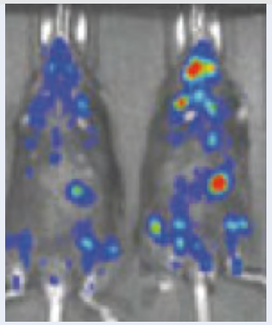
Breast tumors are abnormally organized tissues that contain tumor cells but also supporting cells such as white bloods cells and fibroblasts, and proteins such as collagen. Communication among these different components influences how fast the tumor develops, the likelihood that it will spread to distant organs and its response to therapy. A microscopic imaging method developed by Mikala Egeblad's group allows researchers to watch the interactions between cancer cells and supporting cells in real time in mice with breast cancer as they are being treated with drugs. From the movies thus obtained, the team is learning how these interactions can cause drug resistance, and whether blocking specific interactions between cancer cells and the surrounding tissue will improve sensitivity to drugs.

In a systematic approach to identify genetic factors that make breast cancer cells either vulnerable or resistant to therapy, scientists in Greg Hannon's group are using

WITHOUT TREATMENT



TREATED WITH JQ1



When treated with daily injections of the new drug candidate JQ1, mice with acute myeloid leukemia show fewer signs of disease (red spots) than their untreated counterparts.

RNA interference (RNAi)-based tools that they developed to analyze 100 human cell lines representing a broad spectrum of breast cancers such as, for example, those that are stimulated by estrogen or those that overproduce the HER2 protein. These tools, which the team has made available to the entire breast cancer research community, are also being used to learn more about the genetic characteristics of breast cancer-initiating mammary stem cells, and to find ways of depleting them using microRNAs — a type of small RNA that modulates the activity of genes.

PROSTATE CANCER:

Identifying and treating the serious cases, early

In most cases, prostate cancer is slow-growing and generates few symptoms. Yet 1 case in 100 will rapidly take a lethal course if not treated aggressively. CSHL scientists are developing means of reliably predicting, as early as possible, which cases fall into the urgent category. W. Richard McCombie is involved in a project with collaborators at Memorial-Sloan Kettering Cancer Center (MSKCC) in which the molecular profiles of circulating tumor cells (CTCs) are being determined. Isolated from circulating blood, CTCs potentially contain telltale biomarkers that could help doctors parse patients with treatment-resistant tumors from others, on the basis of a simple blood test. Also in collaboration with MSKCC, Michael Wigler and Jim Hicks are applying their powerful single-cell sequencing method to both CTCs and patient biopsies, to identify prostate cancer biomarkers to guide treatment. Greg Hannon and MSKCC's Charles Sawyers, a CSHL Scientific Trustee, are developing better mouse models of resistant human disease, aiming to obtain a better knowledge of the factors that determine response to therapy.

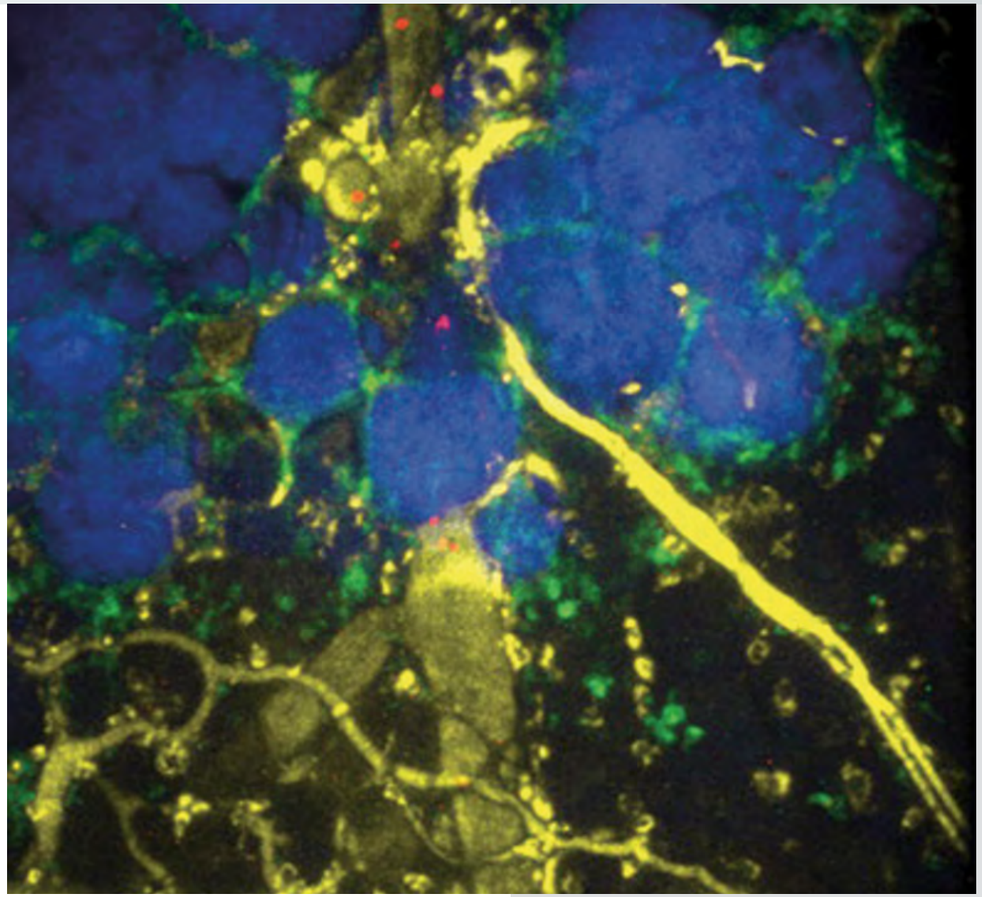
Lloyd Trotman is taking another path toward rapid clinical identification of lethal forms of prostate cancer. He has solved a complex calculus accounting for how the loss of one or two copies of a tumor suppressor gene called *PTEN* either results in prostate cancer or senescence, a state of growth-arrest in which oncogenesis is halted. Recently Trotman has added new permutations to the equation. These involve situations in which prostate cells lose another tumor suppressor, called *PHLPP*, which can act in concert with loss of *PTEN* to produce cancer. He raises the prospect that by monitoring the extent to which the *PTEN* and *PHLPP* genes malfunction, it may be possible to accurately predict whether patients following surgery are on a course to relapse. Checking a patient's "*PHLPP* status" may also help doctors decide on optimal drug treatment strategies, and in the design of more efficient clinical trials.

LEUKEMIA, LYMPHOMA and MELANOMA:

Staging epigenetic interventions

Traditionally seen as a disease caused by genetic changes, cancer is now known also to involve epigenetic changes, which modify the way genes are expressed without altering the DNA code itself. Unlike genetic mutations, disruptions in epigenetic machinery — which can transform normal cells into cancer — are potentially reversible. So epigenetic therapy is now being intensely pursued as one of the most promising anti-cancer strategies. Four FDA-approved epigenetic drugs are already in use.

CSHL scientists hope to add more to the list, starting with Christopher Vakoc, who earlier this year used a novel RNAi-based strategy to discover an epigenetic target for acute myeloid leukemia (AML), an aggressive cancer that is incurable in 70% of patients. This target, a protein called BRD4, allows AML cells to divide in an uncontrolled fashion. By blocking BRD4 with a first-of-its-kind chemical inhibitor, JQ1, developed by collaborator James Bradner of Dana Farber Cancer Center, Vakoc's team was able to suppress aggressive AML in experimental models. With JQ1 expected to enter phase I clinical trials within two years, the collaborators are now pre-clinically developing and optimizing similar drug targets for different genetic subtypes of AML. Because JQ1 and its chemical brethren work by choking off a common cancer-fueling pathway, the hope is that these drugs will work on other forms of cancer as well. The highly successful strategy employed by Vakoc to discover BRD4 is now being adapted to search for therapeutic targets in lymphoma and melanoma.

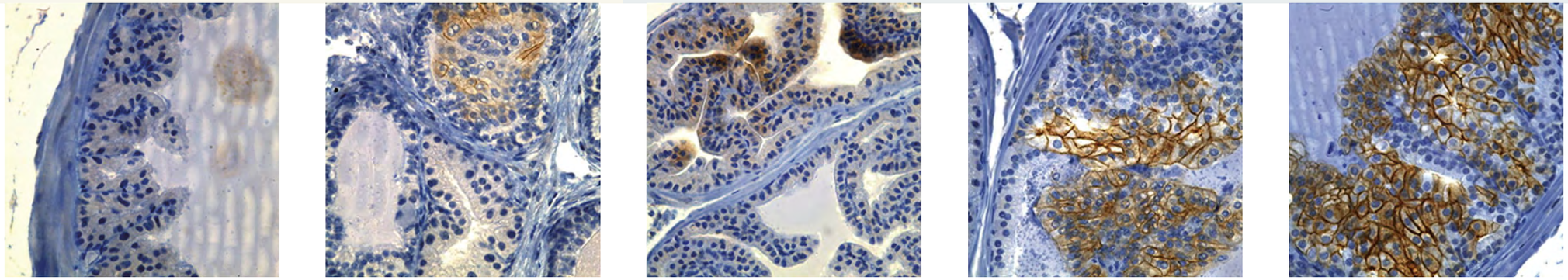


Four-color, real-time imaging of a mouse breast carcinoma shows a tumor with cancer cells (blue), its network of blood vessels (yellow) and two different types of immune cells (red and green).

LIVER CANCER:

New options for targeted therapy

The recent discovery of a therapeutic target, a gene called *FGF19*, by Scott Powers' group, spells hope for more effective liver cancer treatments, which are currently few in number and typically ineffective. An antibody that halts liver tumor growth by blocking the activity of the protein produced by the *FGF19* gene is currently in preclinical development at the pharmaceutical company Genentech. Treatment with this antibody might benefit patients who carry multiple copies of *FGF19*. Powers' group is now pursuing new therapeutic targets and diagnostic markers by examining cancer cells' altered epigenetic landscape, in particular, changes in their pattern of DNA methylation — the tagging of DNA



Prostate tissue samples of five mice, all 8 months old, showing effect of loss of the tumor suppressors *PTEN* and *PHLPP1* in various combinations. Compared with the healthy mouse (far left), the others, moving toward the right, show progressively more pervasive activation of oncogenetic factors (brownish-yellow structures), reflecting increase in genetic damage due to loss of only 1 *PTEN* gene copy (2nd from left) to loss of 1 *PTEN* and 2 *PHLPP1* gene copies (far right).

sequences by methyl molecules. Early data hints at promising candidates within a subset of genes that confer "stemness," or the ability to self-renew — a quality that is repressed in normal adult liver cells.

OVARIAN and CERVICAL CANCER:

Reckoning with cellular and viral culprits

Scott Powers and Alex Krasnitz are translating genomic information generated by the NCI's Cancer Genome Project and other rich data sources into new therapeutic targets for ovarian cancer. As investigators in the NCI's Cancer Target Discovery and Development Network (CTD2), they have analyzed the genomes of over 500 ovarian cancer samples and found "an amazing degree of [gene] copy-number instability." Krasnitz is using "*in silico* cancer genomics" — advanced computational methods of detecting significant patterns — to understand the mountain of tumor data. These have already led to the identification of genome regions harboring recurrent copy-number changes. Over 100 candidate genes have been culled from these regions and are being tested by Powers' team in mouse models of human cancer for their suitability as drug targets. Robert Lucito and Nicholas Tonks of CSHL and others at MSKCC are also integrating genomics and epigenomics to find new ovarian cancer oncogenes and tumor suppressors, whose functional networks are being analyzed with sophisticated computer programs. Separately, Lucito has identified a gene, *CHD3*, whose epigenetic silencing coincides with resistance in ovarian malignancies to the chemotherapy drugs carboplatin and cisplatin. *CHD3* could be a diagnostic marker and future drug target.

Arne Stenlund and Leemor Joshua-Tor have obtained a detailed understanding of the processes that enable papillomavirus (HPV), the virus that causes malignant cervical cancer, to replicate and proliferate. Stenlund hopes to help develop a small-molecule drug that can inhibit HPVs, to help women who don't receive a preventive vaccine and those who are already infected.

LUNG CANCER:

Getting to the bottom of drug resistance

Researchers have puzzled over the confounding ability of cancer cells to develop resistance even to the most powerful targeted therapies. In non-small cell lung cancer (NSCLC), erlotinib, marketed as Tarceva, has provided periods of remission for a subset of patients with a particular mutation, in the gene encoding a cellular receptor called EGFR. Disappointingly, however, nearly all who respond suffer relapses and die within a year or two. Raffaella Sordella's lab, which is working on this problem, has conducted experiments suggesting that some tumor cells may be intrinsically resistant to erlotinib. These cells tend to exhibit features of a transformation called EMT, in which cancerous but non-metastatic epithelial cells that line the lung take on characteristics of mesenchymal cells, which tend to be pro-metastatic. Perhaps the most intriguing quality of the seemingly resistant cells is that they secrete elevated amounts of IL-6, a signaling molecule known to increase inflammation. Clinical trials are under way in which erlotinib is co-administered with antibodies blocking IL-6 to find out whether removing IL-6 from the tumor microenvironment might increase cancer cells' sensitivity to erlotinib.

In other work, Sordella is collaborating with Adrian Krainer to explore the possibility that a process called alternative splicing, in a gene encoding the master tumor suppressor p53, may be involved in a process in which lung cells are prevented from entering a protective state called senescence and instead become cancerous. Sordella is also joining forces with Darryl Pappin of CSHL and Brendon Stiles of Weill Cornell Medical College in a search for biomarkers in NSCLC.

BRAIN CANCER:

Inducing cells to differentiate rather than proliferate

Glioblastoma is the most common form of brain cancer and very difficult to treat. No wonder: malignant glioma cells are notorious for their genetic complexity and heterogeneity; most harbor myriad genetic and epigenetic alterations, which drive tumor initiation and progression. Hongwu Zheng is taking a bold path toward a new form of treatment. In a mouse model of human glioblastoma, his team seeks to force malignant cells to undergo terminal differentiation, hoping in this way to eliminate or reduce the cancer, rather than try to kill the malignant cells outright with toxic chemotherapies.

Medulloblatoma is much rarer, but it's the most prevalent brain cancer afflicting children, and a leading cause of pediatric death. It is thought to begin with the failure of stem-like cerebellar granule cell precursors, or GCPs, to differentiate. Linda Van Aelst and collaborator Mary E. Hatten at Rockefeller University are studying the signaling pathways and extracellular cues that set GCPs on a proper developmental path. This approach has implicated a class of signaling molecules called Rho GTPases, one of which has been found to play a critical role in controlling whether GCPs proliferate or differentiate. They are testing this molecule, DOCK7, in a mouse model of medulloblastoma, while continuing to study how "Rho regulators" exert their effects — important information for future drug development.

PANCREATIC CANCER:

Turning the tables on poor prognosis

A 6-month mean survival time makes cancers of the pancreas among the most lethal. CSHL investigators are obtaining fundamental scientific insights about what distinguishes these lesions, as a basis for effective treatments. Greg Hannon's team studies the role of small RNAs as oncogenes and tumor suppressors and seeks to exploit RNAi libraries they have developed to identify new therapeutic targets. Mikala Egeblad is using advanced microscopy to learn how tumors are affected by surrounding stromal tissue. Robert Lucito looks closely at the genetic irregularities in tumors, and has dissected the mechanism by which overexpresson of a gene called *PAK4* is implicated in the emergence of cancer.

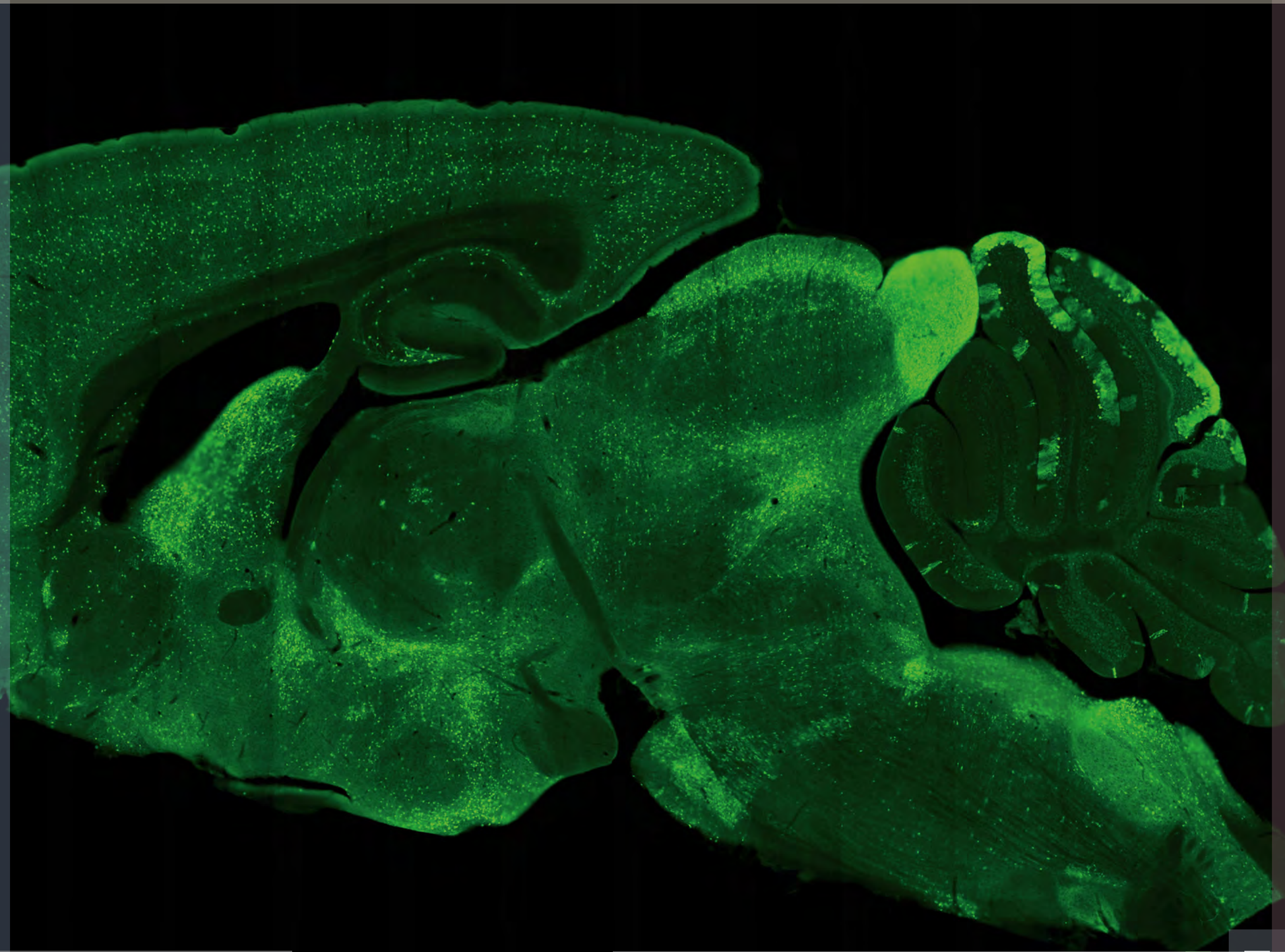
Hema Bashyam and Peter Tarr

One experiment

Professor Josh Huang's team has provided the neuroscience community with a set of powerful new tools that exploit the exquisite specificity of genetics to see and manipulate particular neuronal subtypes in the brains of living, behaving mice.

They have engineered 20 different mouse lines, each containing a genetic "handle" that provides access to a specific cell type. Their quarry: neurons that release the neurotransmitter GABA. Comparatively scarce and poorly understood, GABA neurons play the indispensable role of inhibiting signals sent by much more numerous excitatory neurons. When inhibition malfunctions, a fine balance is upset which may contribute to a range of illnesses such as epilepsy, autism and schizophrenia.

In one experiment, postdoc Hiroki Taniguchi imaged the entire mouse brain, in lengthwise cross-section. The elongated wedge-shaped section at the top is the cortex, with the "S"-shaped hippocampus tucked beneath it. The cauliflower-like cerebellum is at the rear (r) and the knob-like olfactory bulb at the front (l). Each green dot indicates a single GABA cell of a particular type: all in this image contain the neuropeptide somatostatin, labeled to express a green fluorescent reporter molecule. Other GABA subtypes uniquely express other proteins, which make them similarly visible, brain-wide, in other mouse lines. The technology can also be used to make particular GABA cells responsive to beams of colored laser light (optogenetics) or to incorporate deactivated viruses, which enable researchers to observe GABA cells in action in the young brain, forging connections with excitatory neurons. We can expect many discoveries in the period ahead. **Peter Tarr**



It's 4 p.m. Do you know where your kids are?

Many are playing sports and doing homework. But in Flushing, Queens we found an inspired group doing something remarkable: DNA-barcoding forms of life found in the five boroughs!

Empowered by access to sophisticated genomic tools, teenage New Yorkers are exploring the DNA of their surroundings. CSHL's DNA Learning Center is making the URBAN BARCODE PROJECT possible, thanks to a grant from the Sloan Foundation and educational partners across the city.

Team BIG BANG out of Flushing International High School is on the heels of illicit traders of an endangered species. They're scrutinizing the DNA of seahorses sold for medicinal purposes in local Chinese pharmacies. Team members worry that the 2011 World Conservation Union Red List of Threatened Species lists seven seahorse species as "Vulnerable" and one as "Endangered" (there's not yet enough data on 29 others to make an assessment). The students learned that an estimated 24.5 million seahorses are harvested annually and 90% of them are sold in Asian markets, untracked and unlabeled. Are any sold in Flushing's pharmacies among the endangered? Here's where the students' DNA barcoding effort can help.

BIG BANG is one of eight "Urban Barcode Project" teams from this one NYC public school, which was organized to meet the special needs of a community with a large share of recent immigrants. The 9th–12th grade students who voluntarily participate in the after-school science club run by Living Environment teacher C. Anthony Finney and Jordan Wolf come from families that have been in this country for less than three years and have yet to become fluent in the English language.

"We have a majority population of Mandarin Chinese speakers, with a sizable Spanish speaking group. This year, I have speakers of Korean, Haitian Creole, Arabic, Japanese and Tibetan," explains Finney, whose background in biology, political science, scuba diving, and work on the Space Shuttle conjures up Indiana Jones-like movie possibilities.

These kids might be challenged by the English language, but they not only get the science – they say they love it and are eager to see how they match up against teams in from other New York schools. It's about more than bragging rights. The grand prize is a $20,000 scholarship! **Dagnia Zeidlickis**

CSHL's educational partners

Wildlife Conservation Society Prospect Park Zoo

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American Museum of Natural History

The New York Botanical Garden

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RESEARCH PROFILE

Alea Mills

On a cold Sunday afternoon many months ago, CSHL Professor Alea Mills did what many scientists do when facing a grant application deadline — she put off writing and escaped to the lab. A new experiment had just reached a critical stage and she was eager to check on the results, which happened to be a newborn litter of genetically engineered mice.

Throughout her career, Mills has strived to understand human disease by modeling it in mice. When programmed to carry the same genetic abnormalities found in patients with a disease, mice not only become an extraordinarily powerful source of information about the genetic and molecular forces that drive that disease, they can also stand in as test subjects in the development of new diagnostic methods, novel therapies, and better drugs.

Although Mills cut her investigative teeth building mouse models of cancer, the mice that claimed her attention that day had been created with a different human condition in mind — autism. In 2007, Dr. Michael Wigler, also a professor at CSHL, had discovered a link between autism and a small section of chromosome 16. Called 16p11.2, this region has since gained notoriety as a genetic hotspot with links to developmental delay, mental retardation, and schizophrenia.

While about 1% of children with autism have one less copy of 16p11.2 — humans normally have two copies, one inherited from each parent — duplications of this segment have also been found in a few autism cases and more commonly in schizophrenia. But even as these details emerged, one crucial question remained unanswered: were the 16p11.2 copy number variations (CNVs), as these deletions and duplications are called, actually causing autism and the other syndromes?

A "eureka!" moment for autism research

One way to find out would be to check whether clipping out the mouse equivalent of human 16p11.2 or adding more copies of it causes autism-like features to appear in mice. With financial support from the Simons Foundation Autism Research Initiative, Mills used her expertise in a technique called chromosome engineering to do just that.

Invented in the mid-1990s by Mills' postdoctoral mentor Dr. Allan Bradley, the technique involves making a series of precise molecular maneuvers in mouse embryonic stem cells growing in a dish. The cells are then used to create mice that can pass on the engineered chromosome to their progeny. Mills, who helped develop some key shortcuts of this process while in Bradley's lab, had successfully used it before to create cancer and schizophrenia models. But she also knew that "there were no guarantees that we would see anything interesting" this time.

That wintry afternoon, however, one look at the mice gave Mills a "eureka!" moment. The mice that carried one less copy of 16p11.2 "behaved completely different" from the normal mice, which had both copies, and the mice that had an extra copy. Exactly how different would become apparent over the next few months, when Postdoctoral Fellow Dr. Guy Horev set up a one-of-a-kind infrared camera system to track and quantify mouse behavior.

The deletion caused mice to have many of the features used to diagnose autism in children: extreme hyperactivity, difficulty adapting to new environments, sleeping deficits, and restricted, repetitive behaviors. MRI scans of the animals' brains showed that eight different regions of the brain were larger than they should be.

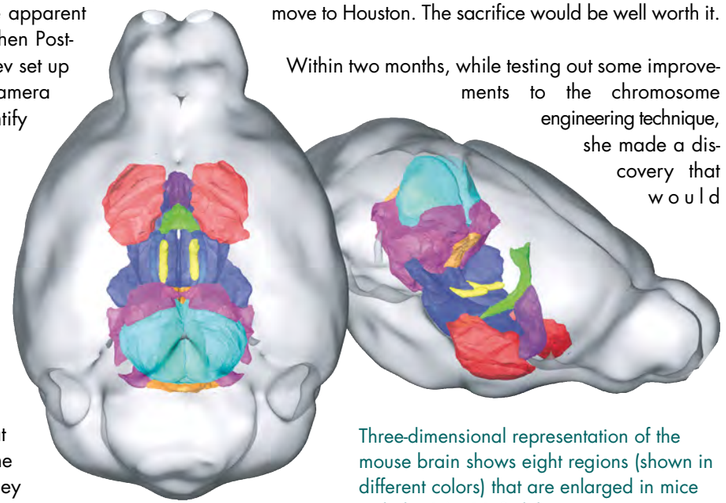
Mills' presentation of these results at a conference at MIT in December 2010 created a huge buzz among the experts that was amplified in the news media when her study was published this October. In addition to all that they might reveal about the biology of autism, the mice can guide Mills and others toward diagnostic markers for autism, and perhaps even point them toward the best mode of treatment — advances that can, among other things, transform the current discussion about autism in society.

Big risks, bigger pay-offs

"If you don't take on high-risk projects that have a chance for a big pay-off, then you're just going to make small, incremental discoveries forever," says Mills. This bold view has served her well during her career, starting with graduate school at University of California, Irvine. There, Mills convinced her advisor Dr. Eric Stanbridge — one of the first proponents of the existence of tumor suppressors, proteins that put the brakes on cancer — to let her develop cancer models using gene-targeting approaches "that no one at the university had tried before."

This experience led to a postdoctoral job offer from Bradley, then based at Baylor College of Medicine in Houston. Mills jumped at the chance to learn from the guru of mouse modeling, even if it meant giving up an enviable California lifestyle on her beloved sailboat to move to Houston. The sacrifice would be well worth it.

Within two months, while testing out some improvements to the chromosome engineering technique, she made a discovery that would



Three-dimensional representation of the mouse brain shows eight regions (shown in different colors) that are enlarged in mice with the 16.p11.2 deletion.

A chromosome-engineered mouse.

open a whole new field of cancer research. That discovery was the *p63* gene, a relative of the famous *p53*, the powerful "master" tumor suppressor. The *p63*-deficient mice engineered by Mills revealed the gene's necessity for the correct formation of limbs and epithelial tissue.

Since her appointment to the faculty at CSHL in 2001, Mills has uncovered *p63*'s role in slowing aging and its ability to control cellular senescence, a form of growth arrest that guards against tumor formation. Her more recent work showing that *p63* produces some protein versions, or isoforms, which suppress cancer and others that promote it, has steered the field in new directions. Earlier this year, her team showed how one of these isoforms stimulates a specific population of stem cells in the skin to form carcinomas, a deadly form of skin cancer.

A second important cancer-related gene that Mills has discovered is one that others had hunted for unsuccessfully for more than 30 years. Looking for this "holy grail" of tumor suppressors, a gene that was known to be missing in many human cancers, was deemed so challenging that Mills couldn't get independent funding to pursue it. But with starter funds from CSHL, where senior staff including President Bruce Stillman firmly backed her work as well as her chromosome engineering skills, Mills's team succeeded in identifying *CHD5* as the elusive tumor suppressor.

Her subsequent work, defining *CHD5*'s role as a circuit breaker that controls the tumor-preventing power inside a cell, continues to have a major impact in the cancer field. CHD5 status — the amount of CHD5 protein a patient has — is now appreciated as a predictor of treatment outcome for cancer patients.

"Because of its supportive atmosphere and its lack of bureaucratic shackles, CSHL is probably the only place where I could have succeeded with this project," says Mills, who encourages a similar free-enterprise type of work ethic within her own group. Her approach seems to have paid off.

At her team's Christmas party last year, postdoc Guy Horev, the behavior analyst working on the autism project, and graduate student Assaf Vestin, working on *CHD5*'s role in living mice, surprised her with a present — the results of an experiment that they had jointly decided to set up. Horev had used his unique camera system to record the *CHD5*-deficient mice. The footage showed some striking, completely unexpected behaviors, hinting at an unexpected link between a cancer-related gene and a neurological syndrome. These are the kinds of paradigm-shifting results spurred by out-of-the-box approaches, and Mills is excited about where this might lead. "When there are no constraints and people work together, research leaps ahead," she says.

Hema Bashyam

A passionate educator

In addition to graduate and postdoctoral researchers, Mills also regularly mentors the youngest scientists at CSHL — high school seniors selected by the Lab's Partners for the Future (PFF) program to spend part of their school year in one of the 50 labs on campus. Mills, who finds the Partners' enthusiasm for learning lab work infectious, is keen to "give them the opportunity to make real contributions to research and advance it."

She also co-teaches a class called Scientific Exposition and Ethics at CSHL's Watson School of Biological Sciences. "We want the students to realize that understanding how their work impacts society and being able to explain their science to the world-at-large in an understandable way is just as important as doing great experiments," she says.

Mills and high school senior Victoria Lellis of Harborfields High School set up an experiment.

Faculty & Friends

Double Helix Medals Dinner raises over $3.3 million

The Double Helix Medal recognizes individuals who have positively impacted human health by raising awareness and funds for biomedical research. Driven by passion, intellect and vision, 2011 honorees Harold Varmus, Kareem Abdul-Jabbar, and Temple Grandin have transformed the way doctors, patients and society approach cancer and autism. More details and images can be found at http://doublehelixmedals.cshl.edu

Faculty & Friends

HHMI appointment for Rob Martienssen

The Howard Hughes Medical Institute (HHMI) and the Gordon and Betty Moore Foundation selected CSHL Professor Rob Martienssen as one of the nation's 15 most innovative plant scientists. The honorees will share $75 million in research funding over five years. Martienssen is a pioneer in unraveling epigenetic mechanisms, which help regulate how genes work, and is an expert on transposons, sequences of DNA that skip around the genome, often altering gene activity.

Brain & Behavior Research Foundation award for Josh Huang

The Brain & Behavior Research Foundation (BBRF) awarded CSHL Professor Josh Huang a NARSAD Distinguished Investigator Grant to study how genetic alterations associated with behavioral symptoms of schizophrenia disturb the development and function of neural circuits. Using a genetically engineered mouse strain, Huang will study chandelier cells, which are key to inhibitory circuits in the brain's frontal areas. NARSAD Distinguished Investigators are selected by BBRF's 124-member Scientific Council.

Early career award for Chris Vakoc

CSHL Fellow Chris Vakoc has been selected by the Burroughs Wellcome Fund to receive the 2011 Career Awards for Medical Scientists. The five-year $700,000 award helps M.D.-Ph.D.s — a unique set of scientists able to connect research to patients — bridge postdoctoral training and the early years of faculty service. Vakoc's award supports his work identifying epigenetic vulnerabilities in chemotherapy-resistant leukemia.

Honorable Patrick Kennedy and CSHL President Bruce Stillman

2011 President's Council highlights

Hon. Patrick J. Kennedy, co-founder of "One Mind for Research," opened the 27th annual President's Council on October 14, greeting donors whose $25,000 gifts support CSHL's most talented young scientists. The retreat focused on "The Science of Addiction" and featured: Susan Foster, Columbia University; Joanna Fowler, Brookhaven National Laboratory; Philip Low, Chairman, Neuro Vigil; Eric Nestler, Friedman Brain Institute and Mount Sinai School of Medicine; and Howard Shaffer, Harvard Medical School. CSHL Assistant Professor Adam Kepecs discussed his work on the neural circuit principles behind decision making, which he hopes will lead to better treatments for diseases such as addiction. Thanks to event chairmen Howard Morgan, Cynthia R. Stebbins and Steve Wiggins.

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CSHL Association

CSHL Association comprises some 1,000 neighbors and friends of the Laboratory who contribute to the Annual Fund, an essential source of unrestricted support for outstanding young scientists. Association members get to know CSHL scientists at lectures, concerts, dinners and other social events that support the Laboratory. Membership levels start at $100 per year. For more information please contact Karen Orzel, Director of Annual Giving and Donor Relations, at 516.367.6886 or orzel@cshl.edu.

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::: **CSHL in the News**

Science Business Exchange
Mouse models of autism
October 20, 2011

Minneapolis Star Tribune
Is gene deletion at the core of autism?
October 17, 2011

Voice of America
Scientists study genetic basis of autism
October 7, 2011

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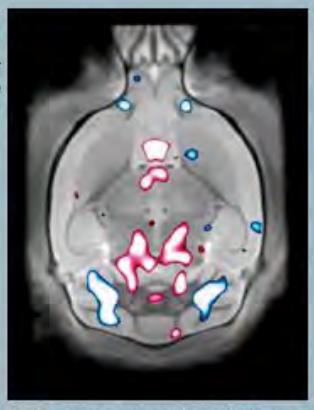
Engineered mice provide autism clues

Professor **Alea Mills**' lab has created a **mouse model** of one of the most common genetic aberrations seen in human autism -- deletion of a small region on chromosome 16 containing 27 genes. In a just-published paper that received wide **media attention**, they provide the first functional evidence that mice inheriting fewer copies of the genes in this region have characteristics resembling those seen in children diagnosed with autism.



Brain regions altered in 'autistic' mice

The team observed that mice with these deletions displayed some of the **behavioral hallmarks** of autism including hyperactivity, difficulty adapting to a new environment, sleeping deficits, and restricted, repetitive behaviors. It's not yet known which of the 27 genes in the deleted region are involved in the observed pathologies, although the team was able to use MRI to identify eight brain regions whose function appeared to be altered in those affected.