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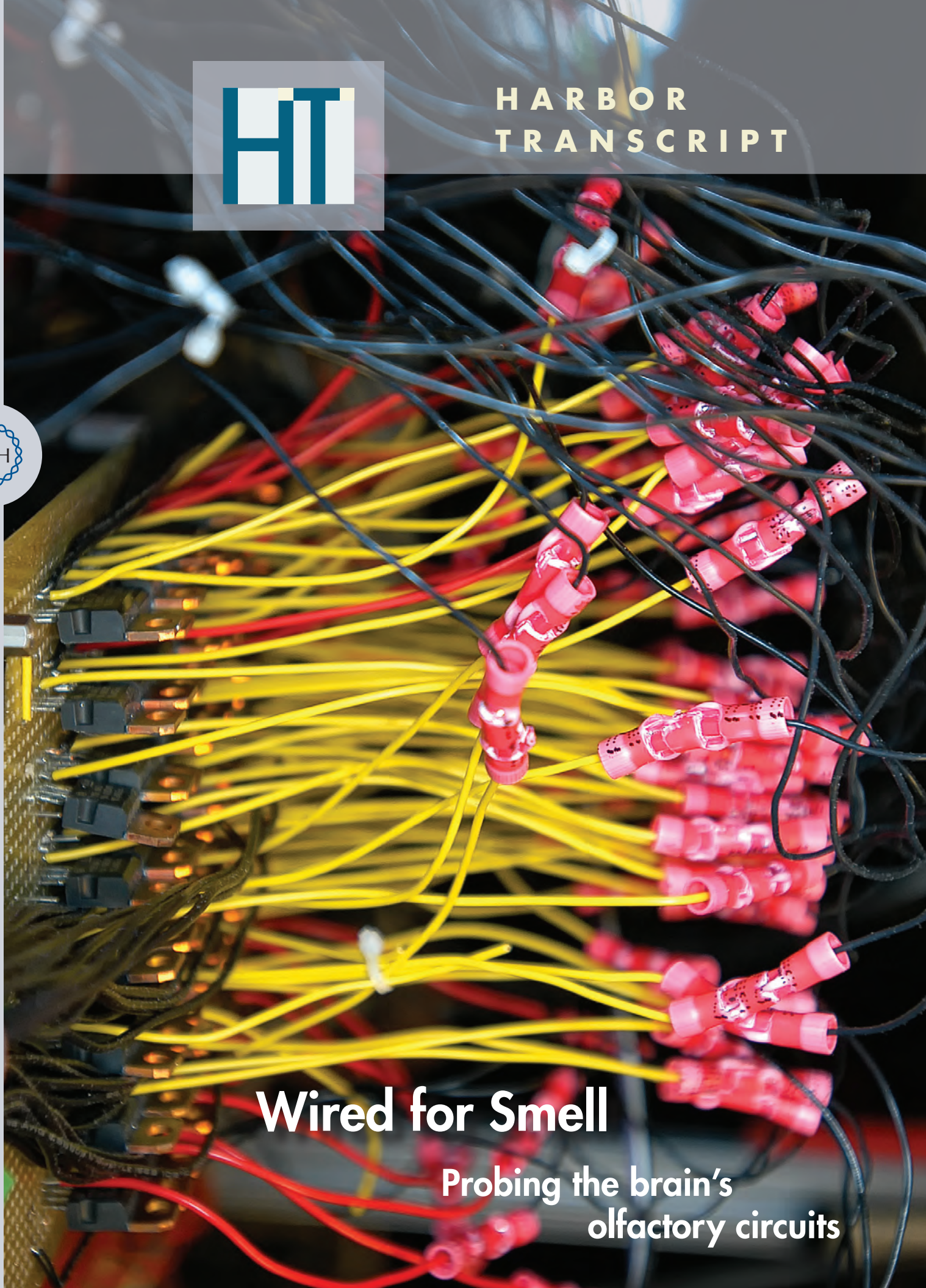

Wired for Smell

Probing the brain's olfactory circuits

COLD SPRING
HARBOR LABORATORY

PRESIDENT'S MESSAGE

This edition of the Harbor Transcript highlights a cadre of CSHL neuroscientists pursuing unique approaches to understanding the brain—a topic so powerful and mysterious that some refer to it as the final frontier of science.

With a growing neuroscience program focused on sensory processing, cognition, and cognitive disorders, CSHL investigators are indeed pushing the frontiers of this field. We are addressing basic questions about sensory representations (auditory, olfactory and visual) and decision-making. Our cognition group uses the tools of modern neuroscience (genetic, molecular, physiology and imaging) to study the neural mechanisms underlying cognitive processes, including attention, memory and decision-making. The cognitive disorder group builds on recent findings about the genetic basis of diseases like autism and schizophrenia to define how neural circuits and synaptic function are disrupted.

I am very encouraged by the increased public attention to brain research. Research has made the brain more accessible and is beginning to reveal the biological basis for mental disorders. Understanding mental disorders as diseases has destigmatized these conditions and allowed society to think more rationally about diagnosis, therapies, and prevention.

The research community is beginning to coalesce around the concept of a collaborative national commitment to neuroscience. Spearheaded by former Rep. Patrick J. Kennedy, the idea of a "moonshot" to conquer brain disease is gaining momentum. I agree with Kennedy that in researching the mysteries of inner space, the human brain, we should apply the same sense of urgency and goal-driven research that allowed us to put a man on the moon. Many of my colleagues at hospitals and research institutions support the premise of "being of one mind for brain research." We agree on the need to focus on the basic science of brain circuits and the genetics of brain illnesses, and to expedite translational research that will bring us new therapies for all neurological and psychiatric disorders. To make it work, we need to achieve an unprecedented level of collaboration across disciplines and institutions, both public and private.

Let's rally behind our passionate neuroscientists and their ambitious goals. Someday, perhaps research will explain why it is that we can do anything we set our minds to.

Bruce Stillman

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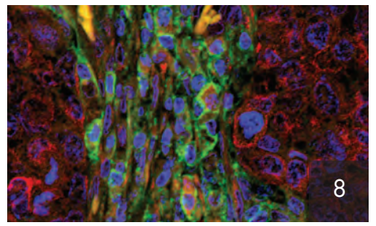
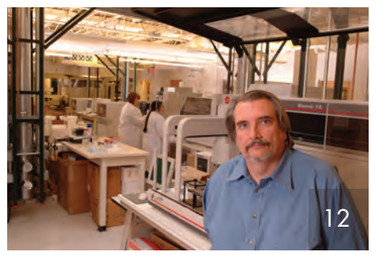
Florin Albeanu and Stephen Shea want to know how mice make sense of smells





FEATURES

FACULTY & FRIENDS

On the cover:
This thicket of wires is part of an apparatus designed by Asst. Prof. Florin Albeanu. It enables his team to deliver precise combinations of 165 chemical odorants to mice, in experiments designed to probe their olfactory circuitry.

Making sense of smell

Four CSHL investigators find in olfaction a window on major brain questions

In an effort to understand neural circuits underlying complex behaviors in people, multiple neuroscience labs at CSHL are probing basic cognitive processes in model organisms, including the mouse and fruit fly. It is research that is providing a foundation for the development of next-generation diagnostics and therapies for neurological and psychiatric illnesses. We focus here on four CSHL investigators who study olfaction separately, but in common pursuit of knowledge about how perception is linked to behavior.

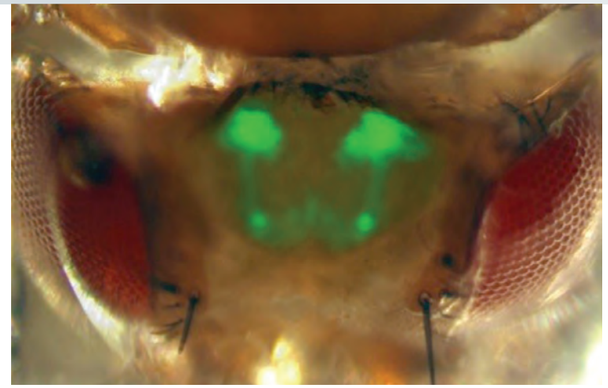
Koulakov: Dimensions of the problem

"Olfaction is the last frontier of our senses, the one that is still almost completely mysterious to us," Alexei Koulakov tells a visitor to his lab, filled with purring computers and diagram-covered whiteboards. An associate professor, he is working on a theory of olfaction, to address a key question: How does the brain of a mammal transform raw sensory inputs into knowledge about the world that can drive behavior?

Koulakov notes we have considerable difficulty describing and defining smells. While we can imagine an infinite range of colors within the band of wavelengths to which receptors in our eyes are sensitive, no olfactory analog is apparent. There is, for instance, no olfactory analog of "red" or "bluish-green." Although we know that humans have 350 different types of olfactory receptors, and we know a great deal about the composition and structure of the molecules that waft about in the air, "we don't really know anything about the internal space, the sensory space, that our olfactory system creates in the brain."

Humans do seem able to classify certain things that are salient, such as "skunk" or "strawberry." But the question is whether these are disconnected perceptions, if they coexist in a single perceptual space, Koulakov says. "This is the big question: is the sense of smell a patchwork, or is there a unifying principle?"

Four on olfaction: (l to r) Glenn Turner, Alexei Koulakov, Stephen Shea, Florin Albeanu



Position of mushroom body (green) in fly's head, in a composite image.

It boils down to a problem of dimensionality. If olfaction is what Koulakov calls a patchwork, it would be necessary to plot human olfaction in 350 separate dimensions—each the product of a separate evolutionary process involving each of the 350 receptor types. Olfaction in mice, creatures that deeply depend on their sense of smell, would occupy a 1200-dimensional space, reflecting their vast number of receptor types. Such a space is something "we have no way of comprehending," says Koulakov.

He hypothesizes, however, that there is an organizing principle behind olfaction. "My research is trying to determine if olfaction is a synthetic sense," he says, "meaning rather than hundreds or thousands of dimensions to understand at once, there might be 10 or 20, each of which would be represented by the activity of some combination of receptors."

> "The big question: is the sense of smell a patchwork, or is there a unifying principle?"
>
> Alexei Koulakov, Ph.D.

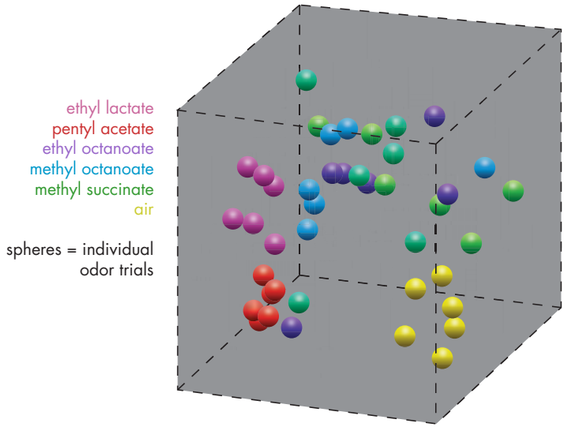
Three of Koulakov's CSHL colleagues are conducting experiments to determine how chemical odorants are represented by neurons, in the olfactory bulb of the mouse and the mushroom body of the fruit fly. This work will show how chemical space maps onto neural space. The next step, says Koulakov, "is to see how the output signal from these neurons propagates to the cortex, where it is processed into percepts" — units of perception, like "citrus" or "gasoline."

Turner: Thresholds between odors

Glenn Turner, an assistant professor, has been looking closely at how odors detected by sensory receptors in the antennae of fruit flies are represented by neurons in a portion of the fly brain called the mushroom body, or MB [see above]. One attraction of the fruit fly is its size. In its MB, there are only 2500 small neurons, called Kenyon cells. "The fact that we can get a fairly complete view of a whole brain area at the cellular level is something you just can't get in a mammal," Turner says. Prior research shows that neurons in the antennae respond broadly to many odors, and yet, the Kenyon cells that receive this raw signal are much more odor-selective, each firing in response to a much narrower range of odors.

Neuroscientists call this sparse representation, and it is a hallmark of the capacity to learn. If neurons respond in a very specific way to specific odors, then memories can be formed and recalled. But how? "When we expose a fly to the same odor over and over, we do not get exactly the same response in the mushroom body," says Turner. "Despite that variability, the animal still knows that it was the smell of an orange. It also knows that different oranges are the same fruit, even though their odors may vary a bit. And, it knows how to tell an orange from a tangerine and a tangerine from a grapefruit or lemon."

Some of Turner's recent work addresses this "threshold" problem of distinguishing one odor from another. The fly has 50 olfactory receptor types, "and while different receptors have different odor 'preferences,' there should be some overlap," he says. In the illustration [next page], five color-coded chemical odorants are listed at the left of the 3-dimensional grey cube, which is a mathematical construct of the olfactory space of a fly, as measured by the firing rates of 60 MB neurons in multiple trials in which the five odors were presented. This representation reduces a 60-dimensional problem by translating the data into three dimensions that we can readily grasp.



Note that dots of certain colors congregate in compact groups, while others don't. Groups that are spatially distinct suggest that the corresponding odorants form distinct representations in the fly's brain.

What amazes Turner is the fact that flies, like people, "seem able to make specific associations with pretty much any odor that comes along." It's a function of having receptors of overlapping sensitivity that sample broadly, yet neural processors that enable discrimination even of very similar odors.

Albeanu: Using light to dissect a circuit

Florin Albeanu, an assistant professor, is studying olfactory circuitry in the mouse brain. Not only does the mouse have 1200 olfactory receptor types; its brain subjects signals coming in from these receptors to a more involved series of processing steps, compared with the fly. Albeanu focuses on the mouse olfactory bulb (OB). Its circuit includes input (from receptors in the nose) and output (to various cognitive areas of the cortex), but it also responds to feedback *from* the cortex as well as slower, neuromodulatory signals from other regions.

Unlike Turner, Albeanu cannot see and take measurements from the totality of the structure he works with; only about 15% of the OB is experimentally accessible in living animals for imaging experiments. Yet this is enough for Albeanu to pursue his aim of "understanding the general principles that transform inputs into outputs in the OB."

As shown in the illustration [next page], inputs into the bulb's glomeruli from odor receptors in the nose are sent on to mitral cells, although only certain ones. Mitral cells are themselves part of a circuit modulated by interneurons. This schema sets up the problem Albeanu and colleagues most recently solved: What do signals from mitral cells connected to the same glomeruli look like, and how does lateral communication, across the layer of mitral cells, modify the output that mitral cells, in turn, send to the cortex?

Albeanu built tools to measure electrical signals in these circuits and to image them. The cells are stimulated by shining beams of colored light into the OB input layer in mice whose glomeruli have been genetically engineered to be capable of photoactivation. By switching the cells "on" and tracing their output, the team can isolate individual mitral cells connected to the same glomeruli, which they call sister cells. Last October they reported on how sister cells vary in their output. "Although synchronized by default, they become offset in their firing with respect to one another as we present odors to the mouse," says Albeanu, "probably because they are modulated by signals coming in from other glomeruli, connected to different receptor-types in the nose."

An interim conclusion: "There are many more information output channels *leaving* the olfactory bulb than the number of information types *entering* it." The work thus revealed a previously unobserved complexity in sensory coding, which Albeanu speculates may help the cortex rapidly make highly accurate odor distinctions.

> "A fly can make associations with pretty much any odor that comes along."
>
> Glenn Turner, Ph.D.

As they begin now to collect data on how mitral cells communicate with the cortex, the team will study how the cortex sends feedback to mitral cells and modulatory interneurons in the OB. They will do these studies "in real time, as the animal is learning something about the environment." For in the end, it's not a problem of simply tracing circuits, but of understanding "how the circuit suddenly, almost instantly, makes sense of a stimulus that it encounters."

Shea: Olfaction and emotional salience

This question of salience is central in the work of Stephen Shea, an assistant professor interested in the olfactory system as a window on social decision-making. Is this sensory system biologically optimized to process data on the basis of its emotional salience? This is pertinent to questions about how the human brain fails to process social and emotional cues in illnesses such as autism and schizophrenia.

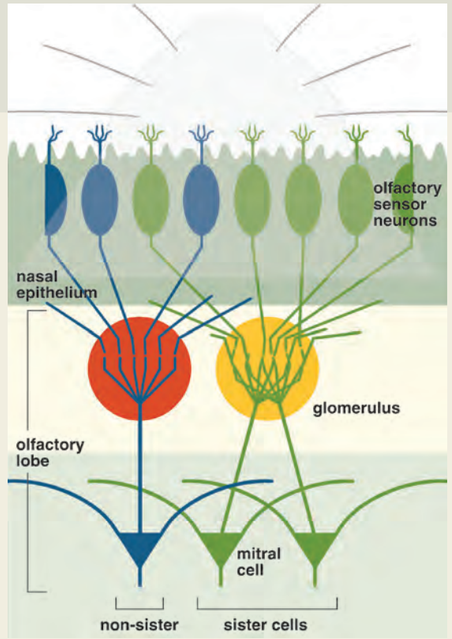
"In order to understand how social cues are perceived and decisions made in the mouse, we need to speak the mouse's language," Shea explains. This language provides mice with ways of detecting, discriminating and remembering one another. Odors, and to a lesser extent vocalizations, enable a mouse to learn, for example, about whether another mouse is friend or foe or wants to mate.

Neurochemicals such as oxytocin and noradrenaline are involved in modulating social decision making in mammals. Produced in the locus coeruleus, in the brainstem, noradrenaline is carried via axonal projections to the mouse's OB. "A mouse is mating, or giving birth or meeting a new mouse—situations in which oxytocin and noradrenaline are released in large quantities. We're studying how that release interacts with information that's arriving at that same time through the olfactory system." It has been postulated that the animal stores or imprints this nexus of signals, biochemically, as the basis of forming an emotionally salient memory.

Shea's team has completed a remarkable set of experiments in which anesthetized mice, exposed to a virtual-reality version of a social encounter, could be shown to "remember" this simulated encounter after waking up. The simulated encounter consisted of introducing the scent of another mouse into the nose of the sleeping mouse. "We were able to effectively create a memory, under conditions in which we could study neural manifestations of the process."

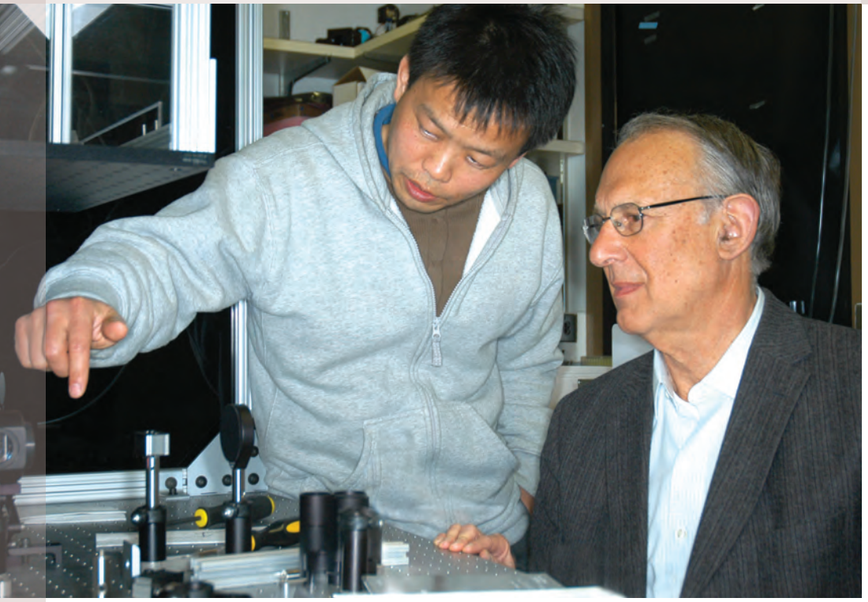
Shea's lab is now perfecting means of recording from awake animals, which will enable them to show this olfactory-centered memory-formation process occurring in the context of natural behavior. Preliminary clues are intriguing: mice have been shown to respond to individuals they remember via olfactory memory by showing less interest, which correlates with reduced mitral cell firing rates. An encounter with a new prospective mating partner produces the opposite result. "We hypothesize the sensory information is sent downstream to deeper brain structures, where some interpretation or behavioral decision is made," Shea says.

The picture of olfaction that emerges in these four CSHL labs—from the uptake of raw sensory data, to the recognition of patterns, to the formation of percepts, to the imprinting of their salience at particular moments in time—inspires a sense of awe over what even simple brains can do. It also makes a vivid case for the value of research on model organisms, work that has placed us on a path toward understanding the brain dysfunctions underlying some of the most perplexing and devastating human illnesses. **Peter Tarr**



The mystery addresed by researchers is how signals from sensors in the nose are recognized and processed by successive brain layers to form perceptions that a mouse can act upon.

On depression's trail



Bo Li and Fritz Henn are studying depression's neural circuitry

More than 20 million Americans will leave their doctors' offices this year with prescriptions for antidepression drugs, dozens of which now line pharmacy shelves. No one knows precisely how these drugs combat depression's symptoms. Why they and other modes of therapy often fail is also unknown, sending neuroscientists in search of depression's neural circuitry within the brain and ideas for better, safer treatments.

At CSHL, Professor Fritz Henn and Associate Professor Bo Li are focusing on a tiny, triangular region in the midbrain called the lateral habenula (LHb), which acts as a junction box for signals that pass between the forebrain and other brain areas. Henn and Li's recent discoveries, published in the journal *Nature* (February 2011) suggest that the LHb might be the key to finding new treatments that could help even severely depressed patients who fail to respond to standard therapies. The scientists have found that when neurons in the LHb are hyperactive, they signal "disappointment" by crippling the brain's reward system. As Henn puts it, "What could be more depressing than that?"

Homing in on the habenula

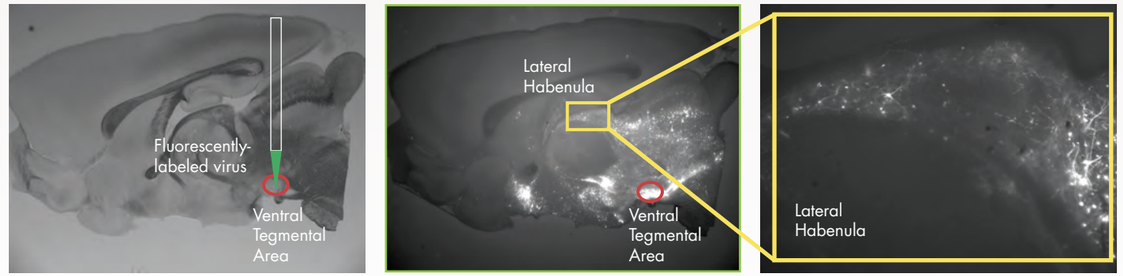
The CSHL team is exploring the link between the LHb and depression in rats that exhibit "learned helplessness," a set of human-like depressive behaviors stemming from a perceived absence of control over a given situation. These animal models were developed over the last two decades by Henn, who until last year co-directed life sciences research at Long Island's Brookhaven National Laboratory. In contrast to normal rats that do whatever it takes to escape physical, life-threatening challenges, the "helpless" animals just give up and suffer passively.

A few years ago, a study that compared these rats to those resilient to stress—Henn calls these die-hards the "New Yorker rats"—revealed a striking difference in the level of metabolic activity in just one brain region, the LHb. "Two studies by other groups had previously hinted at a connection between 'helpless' behavior and the habenula," explains Henn. "I wanted to prove this link and define the underlying mechanisms."

To do that, Henn approached then-CSHL scientist Robert Malinow and his postdoctoral researcher Bo Li, who were just a few exits away on the Long Island Expressway. The duo also were, according to Henn, "the best team in electrophysiology," a method that allows scientists to eavesdrop on neuronal chatter by measuring electrical activity in neuronal synapses—the gaps between connecting neurons.

"Many brain areas had been implicated in depression," recalls Li. "But Fritz convinced us that the LHb was a critical target." This proved to be true right away. Li's very first recording of neuronal activity showed that the LHb neurons in depressed rats were markedly more active than in stress-resistant rats. Finding that the hyperactive LHb neurons in turn dampened the brain's reward system, "We hypothesized that if this hyperactivity occurred too often or for too long, it might not just be about disappointment anymore but rather, might cause pathology," explains Li, who accepted a faculty appointment at CSHL in 2008.

In support of this idea, the scientists found that delivering high-frequency electric pulses via electrodes inserted into the LHb (but not adjoining brain areas) of the helpless rats



When injected into a downstream target region called the ventral tegmental area (VTA), a fluorescently labeled virus illuminates depression-related neurons by entering nerve endings in the VTA and traveling to the nerves' point of origin in the lateral habenula (middle and right panels).

undid this reward-dampening effect and reduced the rats' depression-like behavior. This method is analogous to deep brain stimulation (DBS), which has helped people with Parkinson's and some with clinical depression as well.

Having used it successfully in one patient, Henn—an experienced clinical psychiatrist—is now collaborating with doctors in Germany and New York's Mount Sinai Hospital to test whether the LHb is a better target for DBS than other brain areas. Henn and Li are setting their sights on other breakthroughs, too. As Li says, "DBS is a great research tool for discovering things about depression in animal models. But for the millions of people suffering from treatment-resistant depression, there needs to be a non-invasive, less dangerous alternative."

Solving a circuit problem

To find this alternative, Henn and Li must learn what drives the hyperactivity in the LHb; identify the targets that the LHb neurons project onto and alter in depressed animals; and ultimately, manipulate the circuitry of the LHb to halt depressive behaviors.

The LHb gets its input both from the brain's limbic system, where emotions are processed, and the prefrontal cortex, which is the brain's cognitive area. The LHb adds it all up and produces an output that affects almost all brain functions. "I think that it's this addition process in the habenula that gets jumbled up in depression," says Henn. "That's where the pathology might lie."

The team's early experiments suggest that the input that triggers LHb hyperactivity might come from the brain's glutamatergic system—a neuronal network switched on by glutamate, a powerful neurotransmitter. When glutamate molecules released into a synapse by a pre-synaptic neuron activate a post-synaptic neuron, helper cells called astrocytes end this transmission by soaking up the glutamate. Henn is testing the idea that defects in the astrocyte re-uptake system might lead to LHb hyperactivity and depression.

Output from the LHb controls the brain's three major neuromodulators: dopamine (reward system); noradrenaline (anxiety/fight/flight response); and serotonin, which mediates a host of emotional states and is the target of almost all antidepressants available today. "But we don't know which of these pathways are affected in depression and how the target neurons alter their activity in response," explains Li. "To be able to design accurate, behavior-altering drugs, we need first to do detailed molecular studies on these neurons to understand how they're different in depression."

Li is pursuing this goal with support from the Dana Foundation and a Biobehavioral Research Award for Innovative New Scientists (BRAINS) from the National Institute of Mental Health. His methods blend classic techniques of molecular genetics and neurobiology with optogenetics, the latest innovation in molecular manipulation in which scientists use light to control the activity of individual neurons.

Working closely with other CSHL neuroscientists, Henn and Li have assembled a formidable arsenal of tools: genetically modified animals that carry light-responsive genes in their depression circuits; genetically manipulated viruses that light up entire chains of nerves and thus help trace the pre-synaptic origins and the post-synaptic targets of hyperactive LHb neurons (see image above); and more.

Although it is complex and time-consuming, defining the contours of depression's neural circuit and its components "is crucial if we are to develop more effective treatments for depression and other mood disorders," says Henn. The statistics of depression certainly bear out the urgency of Li and Henn's mission. The World Health Organization's (WHO) Global Burden of Disease project predicts that by 2020 it will become the second leading cause of illness worldwide. **Hema Bashyam**

One experiment

Appearances can be deceiving. This image, made by graduate student Matthew Camiolo in the lab of Assistant Professor Raffaella Sordella, seems as captivating as a stained glass window. In fact, it takes us to a cellular battleground the size of a pinhead within a human lung cancer tumor. It's part of one experiment now underway in the Sordella lab, whose members are seeking to understand what makes certain tumors resistant to targeted therapy and what mechanisms lead some cells to become metastatic.

In prior studies, Sordella's lab noticed differences within lung cancer and lung cancer-derived cell lines. Some cancerous epithelial cells had acquired new features and changed their appearance from round to elongated. Importantly, these cells were resistant to the drug Tarceva (erlotinib). The team developed a series of stains that make visible what they postulate are useful markers of this transformation, called an epithelial-to-mesenchymal transition, or EMT.

The team is currently moving closer to decoding the master regulatory mechanisms that govern this switch toward EMT. In this image, the central mass of round epithelial cells with red borders and blue nuclei are cancerous but haven't undergone the transition. But in a looping arc surrounding these cells we see oblong cells, yellow and green in hue. Green indicates an abundance of the cell-surface marker CD44, characteristic of mesenchymal-like cells. Yellowish cells express both CD44 and a marker, colored red, expressed by all tumor cells. In correlating the observed staining pattern with tumor status and linking that to prognosis, this research will lead to efforts to develop new diagnostics. It may also inform efforts to develop new drugs able to selectively kill cells showing the marks of EMT or repress their ability to detach from the primary tumor mass and colonize other sites in the body. **Peter Tarr**

Watson School 2011 graduates

Amy Rappaport

Cornell University
National Institute of Health Predoctoral Trainee and Barbara McClintock Fellow
"Dissecting tumor suppressor and tumor maintenance genes in poor prognosis acute myeloid leukemia "

Drawn to pursue a Ph.D. at the Watson School by CSHL's "intense, collaborative scientific environment," Rappaport says that her thesis work in Howard Hughes Medical Institute Investigator Scott Lowe's laboratory benefitted immensely from her interactions with "brilliant and passionate postdocs and clinical fellows.".

Rappaport's research has revealed critical molecular and genetic interactions that underlie progression of a type of acute myeloid leukemia (AML) that has poor prognosis. Combining genetic analysis of human samples, mouse cancer models and RNA interference technology—a cutting-edge way of studying gene function—Rappaport has identified potential drug targets as well as strategies for effective targeted therapies for AML. She heads to a postdoctoral fellowship at the biotech company Genentech in San Francisco where she will continue to investigate cancer and find ways to combat it.

Claudio Scuoppo

University of Turin, Italy
Curt Engelhorn Scholar - The Angel Foundation
"Architectural models of tumor suppression in lymphoma"

Scuoppo's desire to understand the genetics of cancer dates to his pre-graduate school days when he worked at the University of Turin, Italy on an aggressive childhood cancer and the genes that cause it. During his thesis research in Professor Scott Lowe's lab at CSHL, Scuoppo identified nine genes that do the opposite—suppress cancer. Scuoppo found the tumor suppressors, as these genes are called, by first analyzing samples from patients with lymphoma and then modelling the loss of candidate genes in a mouse model of lymphoma. Focusing on two of the genes, he discovered a new tumor suppression mechanism and how lymphomas evade it to survive and grow.

"I'll never forget the feeling of excitement that derives from being constantly exposed to new and provocative ideas at CSHL," he says. His experience has motivated him to "keep finding future projects in which I can develop new ideas that significantly impact the lives of cancer patients."

Hema Bashyam

RESEARCH PROFILE

W. Richard McCombie

Advances in sequencing technology are revealing the genetic basis of human disease

In a cavernous room within CSHL's Woodbury Genome Center, 16 machines somewhat larger than the average dishwasher are cataloging the sequence in which the four DNA "letters" or chemical bases—A, T, G, C—appear in an organism's genetic code, or genome. At the moment, some machines are sequencing the genomes of prostate cancer patients; others, the genomes of people with bipolar disorder and depression. One is even sequencing the genome of wheat, which at six times the size of the human genome presents quite a decoding challenge.

As the overseer of these projects and a few others, Professor W. Richard McCombie is CSHL's sequencer-in-chief. He is at the leading edge of a technological front, which in the last few years has begun moving so fast that it's "allowing us to think of questions and study them in ways that weren't feasible even a month ago," he enthuses. As a result, his team is forging ahead in two ways: pushing "next-generation" sequencing technology to spell out new genomes faster, cheaper and with greater accuracy; and using this data to advance our understanding of the role of genetic and epigenetic variations in cancer and cognitive disorders such as schizophrenia and bipolar disorder.

These variations—person-to-person differences in DNA and its chemical tags, respectively—play a role in whether an individual has a higher or lower risk of getting a particular disease. When McCombie and his colleagues have crunched through the millions of megabytes of DNA data generated by those 16 machines, their findings will help unlock a universe of information critical for improving human health.

The incredible power of genomics

McCombie's interest in disease-related genetics goes back to the early 1990s when he joined the National Institutes of Health (NIH) after a brief stint in the biotechnology industry. Trying different approaches to understand the genetics of Huntington's disease, "We still failed to get very far, despite being at the cutting edge of sequencing," McCombie recalls.

And cutting edge it certainly was. McCombie's boss at the NIH was J. Craig Venter, who would soon embark on the race that led to the first complete human genome sequence. Initially tasked by Venter to improve biochemical and molecular methods of studying cellular receptors in the brain's neurons, McCombie soon veered toward DNA sequencing. A 1982 paper that he had read as a Ph.D. student at the University of Michigan had etched a deep impression on him.

The paper, by Frederick Sanger, who won his second Nobel Prize for inventing DNA sequencing, laid out the DNA sequence of a virus called lambda. "The paper explained a huge amount of the virus's biology by just referring to its sequence," McCombie remembers. "It struck me that having a genomic sequence gave one an incredible power to understand an organism's biology and link its genetics to any problem." But he also realized that sequencing at the time was "neither fast nor large-scale enough to really make an impact."

By the time CSHL recruited him in 1992, McCombie had made significant headway at the NIH in addressing both of these drawbacks. He led one of the first groups ever to carry out automated sequencing of genomic DNA on a major scale. And he helped Venter organize the first large-scale project involving Expressed Sequence Tags (ESTs)—tools that have since been used to identify thousands of genes and predict their function.

Illumina sequencing machines in Richard McCombie's lab are decoding genomes of patients with cancer and cognitive disorders.

A decade of genomic "firsts"

These triumphs would serve McCombie well at CSHL. At a party for CSHL's Richard Roberts, who had just won a Nobel Prize, a chance conversation between McCombie and plant geneticist Rob Martienssen about sequencing triggered a hugely successful partnership. In 1996, with funding from the National Science Foundation, the duo formed one of three teams in the country that began to sequence the first plant genome —of *Arabidopsis thaliana* (mustard plant), a workhorse in plant genetics labs.

Propelled by a change in technology—from "gel-based" sequencing to "capillary-based" sequencing—the team finished the project in 2000, two years ahead of time. Around the same time, as capillary sequencing "leapt ahead by a couple of generations," a CSHL group led by McCombie joined an international research consortium to sequence the mouse genome. And in 2001, team CSHL made history as one of 20 groups to collectively publish the first draft of the human genome.

McCombie's next challenge was harder: sequencing crops like corn and rice. Not only are their genomes much larger than that of humans, they are stuffed with chunks of so-called repetitive DNA that are difficult sequence and contain few genes. With funding from the U.S. Department of Agriculture, McCombie and Martienssen developed a method—called methylation filtration—to capture only the gene-rich regions. With this shortcut, they rapidly sequenced part of the corn genome in 2003 (its complete genome was published in 2009). They also helped sequence the entire genome of rice in 2005.

Finding the mutations that cause disease

That's when, McCombie says, technology changed yet again, advancing genomics by a factor of 10 annually (in contrast to computing, which according to Moore's law, advances by a factor of 1.5 per year). Invited to sit in on a meeting between then-CSHL President and DNA pioneer Dr. James D. Watson and the founders of 454 Life Sciences, a company that wanted to sequence Watson's genome, McCombie recognized the 454 platform as a potential game-changer.

Realizing that "we were about to enter a different world in which sequencing could help find the causes of disease," he began to think about ways to extract and sequence small stretches of the human genome; for example, regions that actually code for protein (now known to be about 2% of the genome) and so are likely to harbor mutations that contribute to disease. The result was a revolutionary method that McCombie and CSHL molecular biologist Gregory Hannon developed in 2007 called targeted resequencing.

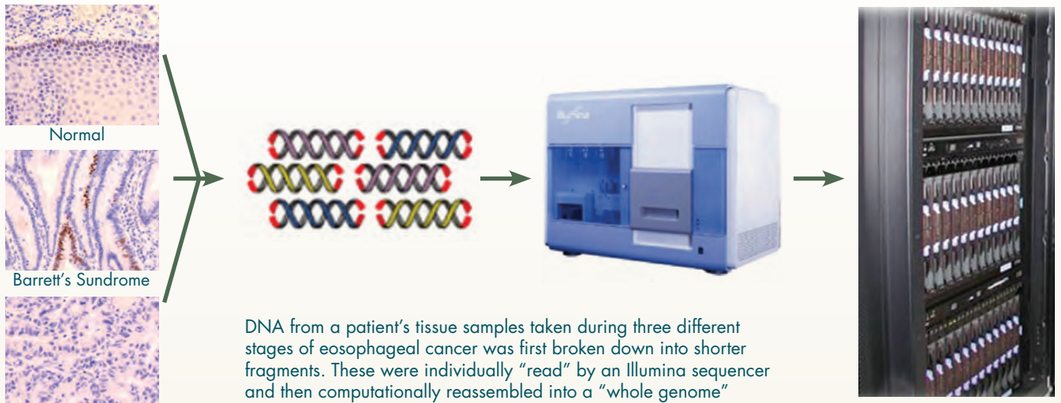
This method has made it possible to sequence and compare genomes, at low cost, of large groups of people, which is key to unearthing insights about disease-causing mutations. CSHL scientists have used it to home in on cancer-related genes as well as study entire "exomes," the totality of coding regions within a genome.

With support from the Starr Foundation, McCombie's group and their collaborators at Memorial Sloan-Kettering Research Center in New York are now examining tumor cells in the blood of prostate cancer patients on chemotherapy to find genetic markers that determine response to therapy. They are also studying, sequencing and analyzing genomic DNA from a patient with eosophageal cancer from samples taken before, during and after tumors grew [image above]. "Studying the genetics of cancer progression this way wasn't feasible even a couple of years ago," says McCombie.

These technological innovations have dovetailed with a dramatic surge in sequencing power at CSHL. The acquisition of next-generation sequencing platforms has boosted output from 78 million DNA bases per month in 2000 to 2.5 trillion bases per month in 2011. The costs of whole genome sequencing are plummeting too. Between 2008 and 2011, there were two 50% drops each year. In February 2011, it cost CSHL $25,000 to sequence a genome. By summer 2011, McCombie expects it to cost no more than $ 6,000.

Such advances have spurred scientists elsewhere to sequence their own and others' genomes, but McCombie isn't tempted to follow suit. "In the absence of a diagnosis of a disease like diabetes or cancer, I'm not sure personal genome sequencing has a cost benefit," he reasons, but admits to thinking about it. "All studies need positive controls," he says. "I wouldn't rule out including myself as one someday." **Hema Bashyam**

Tracking cancer's evolution with whole genome sequencing



DNA from a patient's tissue samples taken during three different stages of eosophageal cancer was first broken down into shorter fragments. These were individually "read" by an Illumina sequencer and then computationally reassembled into a "whole genome" sequence.Comparing this sequence to a reference genome identified genetic alterations that occurred as the cancer progressed.

Genomics unravels cognitive illnesses

Encouraged by Dr. James Watson, philanthropists Vada and Ted Stanley donated $25 million to launch the Stanley Institute for Cognitive Genomics at CSHL in 2007. Under McCombie's Directorship, the Institute is poised to translate findings about the genetics of cognitive disorders into DNA-based diagnostic tests by 2017.

It's now apparent that the mutations responsible for these disorders are rare variations in DNA caused by losses and/or gains of large chunks of DNA sequence (called copy number variations or CNVs) or by changes in single DNA nucleotides. CSHL's advances in next-generation sequencing "have made it possible to drill these disorders down to the single- nucleotide changes that lead to disease symptoms," says McCombie.

With scientists at the University of Edinburgh, McCombie's group recently sequenced the complete genomes of five members of a large Scottish family (135 members) in which many suffer from bipolar disorder or depression. "After identifying all variations among them, we believe we will be able to link these to the presence or absence of disease," McCombie explains. The scientists have also sequenced DISC1—a gene disrupted in another large family with psychiatric disorder—in about 2000 individuals, half of whom have schizophrenia, bipolar disorder or depression. Analysis is underway of the thousands of variants found to pinpoint the rare disease-causing ones.

Scientists are rock stars!

The April 9 "Labapalooza!" experiment proves it. More than $150,000 was raised in support of CSHL's youngest and brightest investigators. The evening featured two dozen scientist-musicians in seven bands and ensembles including Jellyfish Explosion & Friends [image above], AC/TG and the Young and The Restless!

Rock stars who double as CSHL scientists include vocalist Emily Hodges, Ph.D., who developed the array capture resequencing technology that facilitated the discovery that modern humans are incredibly similar to Neandertals at the level of the proteome—the full set of proteins that our genes encode.

Research Investigator Shane McCarthy, Ph.D., another rocker, has helped show that rare mutations can increase the risk for schizophrenia and autism. By day, guitarist Luke Dow, Ph.D., is focused on finding ways to exploit the mutations in tumor cells to develop more targeted and effective therapies for colon cancer and melanoma.

Labapalooza! showcased notable Long Island painters, sculptors and photographers, including David Peikon, Rachel von Roeschlaub and William B. Jonas, who donated proceeds from the sale of their pieces.

Long Island's finest food establishments—Besito, Birch Hill Market, Fiorello Dolce, Messina Market, Nisen Sushi and Rothmann's Steakhouse, Sterling Affair Caterers—offered guests a sampling of specialties.

The Laboratory thanks Cold Spring Harbor Laboratory Association Directors and event co-chairs: Michele Celestino, Nelson DeMille, Ginny Knott, Laureen Knutsen, Tim O'Neill, David Peikon, Tracey Serko, Heather Spehr, and President Sandy Tytel. This uniquely successful feast for the eyes, ears and palate would not have been possible without generous sponsorship from CSHL friends and neighbors. You rock!

Faculty & Friends

Hannon wins regional graduate school mentor award

Howard Hughes Medical Institute Investigator Greg Hannon was honored on April 15 with the Northeastern Association of Graduate School Geoffrey Marshall Mentoring Award.

The Mentoring Award recognizes outstanding support of graduate students, from course completion through research and placement. Since the Watson School of Biological Sciences opened its doors in 1999, Dr. Hannon has mentored a total of 12 postdoctoral fellows and 17 graduate students. The achievements of his trainees have been consistently outstanding.

Northeastern Association of Graduate Schools

Four of his students completed their degrees in less than four years and two were recipients of the prestigious Harold M. Weintraub Graduate Student Award. Many others have received awards under his direction, including the L'Oreal UNESCO For Women in Science Award, the National Science Foundation Graduate Fellowship and The Howard Hughes Medical Institute Graduate Fellowship.

Every mentee in his lab has published in a high-impact journal, with more than 60% of his own 200+publications having mentee authors. Three of these publications received recognition in the journal *Science* as the "Breakthrough of the Year."

The mentorship Dr. Hannon provides has resulted in the placement of 10 of his graduate students in prestigious postdoctoral positions, with four already holding independent faculty positions, at Mt. Sinai School of Medicine, the University of Toronto, Fred Hutchinson Cancer Research Center, and the Whitehead Institute.

NIH New Investigator Regional Conference

If a solid research plan is the crucial requirement for launching a career in academic research, then securing funding for that plan is the crucial requirement for sustaining that career, especially in the climate of squeezed federal budgets. With that in mind, CSHL and the National Institutes of Health (NIH) co-hosted the "NIH New Investigator Regional Conference" on March 14.

Supported by the Alfred P. Sloan Foundation, the event, held at Grace Auditorium, brought key NIH scientific program leaders together with more than 250 new faculty from 56 universities and research centers to discuss national biomedical research priorities and issues facing new investigators.

"In spite of NIH programs designed to facilitate the transition of new scientists to independently funded principal investigators, the average age at which an investigator first obtains an initial independent research grant remains unacceptably high," says Dr. Walter Goldschmidts, Executive Director of Sponsored Programs at CSHL.

ALFRED P. SLOAN FOUNDATION

"The exchange of ideas between the participants, NIH and institution presidents made it clear that there is a need for this interaction," said Goldschmidts, who hopes to enhance and expand the meeting nationally.

Faculty & Friends

WSBS 2011 Honorary Degrees

At the May 1 Commencement Convocation of the Watson School of Biological Sciences, honorary degrees were conferred upon Professor James R. Lupski, M.D., Ph.D., Department of Molecular and Human Genetics, Baylor College of Medicine, and James Simons, Ph.D., founder of Renaissance Technologies LLC.

Dr. Lupski was honored for his work on the consequences of genomic alterations in human disease. He is an alumnus of the CSHL Undergraduate Research Program and is a role model for students. According to Dr. Lupski, "central to our understanding of human biology, evolution, and disease is an answer to the following questions: What is the frequency of *de novo* structural genomic changes in the human genome? What are the molecular mechanisms for genomic rearrangements? And what is the genomic code?" In 2010, as a result of pursuing these questions, Dr. Lupski published the successful outcome of using whole-genome sequencing to find the mutations responsible for a disease from which he himself suffers—a neurological condition called Charcot-Marie-Tooth (CMT) disease—which results in muscle weakness and wasting.

Dr. James Simons was honored for his contributions to mathematics, science and human health. CSHL is grateful for the tremendous support that he has provided to establish the Simons Center for Quantitative Biology at CSHL and for Dr. Simons' ongoing facilitation of collaborative science on Long Island. Dr. Simons is currently President of Euclidian Capital and Board Chair of Renaissance Technologies, a highly quantitative investment firm. He has also been chairman of the Mathematics Department at Stony Brook University and a cryptanalyst at the Institute of Defense Analyses in Princeton. His scientific research was in the area of geometry and topology, in discovering and applying certain geometric measurements, now called the Chern-Simons invariants, which have wide use, particularly in theoretical physics.

Stillman honored with Louisa Gross Horwitz Prize

On February 17, CSHL President Bruce Stillman accepted the Louisa Gross Horwitz Prize for seminal work in which he and his colleagues have elucidated mechanisms involved in the process by which DNA, the genetic material contained within the nucleus of nearly all our cells, replicates itself. He shared the prize with Thomas J. Kelly, M.D., Ph.D., director of the Sloan-Kettering Institute at Memorial Sloan-Kettering Cancer Center.

"These two investigators, more than any others, are responsible for discovering the key molecular players in and the principles that govern the process of genetic replication," said Wayne A. Hendrickson, Ph.D., chair of the Horwitz Prize Committee and professor of physiology and cellular biophysics at Columbia University. Hendrickson added that Stillman and Kelly have given science a much needed understanding of the way cells work in humans, in so doing shedding light not only on the duplication of normal cells but also how the process goes awry in cancer.

The Louisa Gross Horwitz Prize has been awarded annually since 1967 by Columbia University, for outstanding basic research in biology and biochemistry. Forty-two of the 82 awardees, to date, have gone on to win the Nobel Prize.

Genome Technology's Annual "Young Investigator" List

CSHL Assistant Professor Michael Shatz, 2010 WSBS graduate Yaniv Erlich, and Nick Navin, who completed his graduate work in Mike Wigler's laboratory at CSHL, were judged by leaders in Systems Biology as three of the brightest young minds in that field today. *Genome Technology* magazine's 5th annual Young Investigator competition recognized Dr. Shatz for his work on Genome Assembly and the Cloud. Dr. Erlich, who is now a Fellow at the Whitehead Institute for Biomedical Research, was recognized for his work in Fast-Paced Bioinformatics. Dr. Navin, now Assistant Professor at MD Anderson Cancer Center in Texas, made the list for his work on The Evolution of Cancer Tumors.

Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

2011 Cultural Series

Upcoming public lectures @ Grace Auditorium

7:00 PM
22 June Wed

New Research and Approaches to Depression and Bipolar Disorder

Co-sponsored by St. Johnland Nursing Center, The Brain & Behavior Research Foundation and Cold Spring Harbor Laboratory

3:00 PM
23 Oct Sun

Music: How It Can Rewire Your Brain

Co-sponsored by St. Johnland Nursing Center and Cold Spring Harbor Laboratory

For additional information on events in the Cultural Series, visit online: **events.cshl.edu**.

For information about Cold Spring Harbor Laboratory, visit: **www.cshl.edu**.