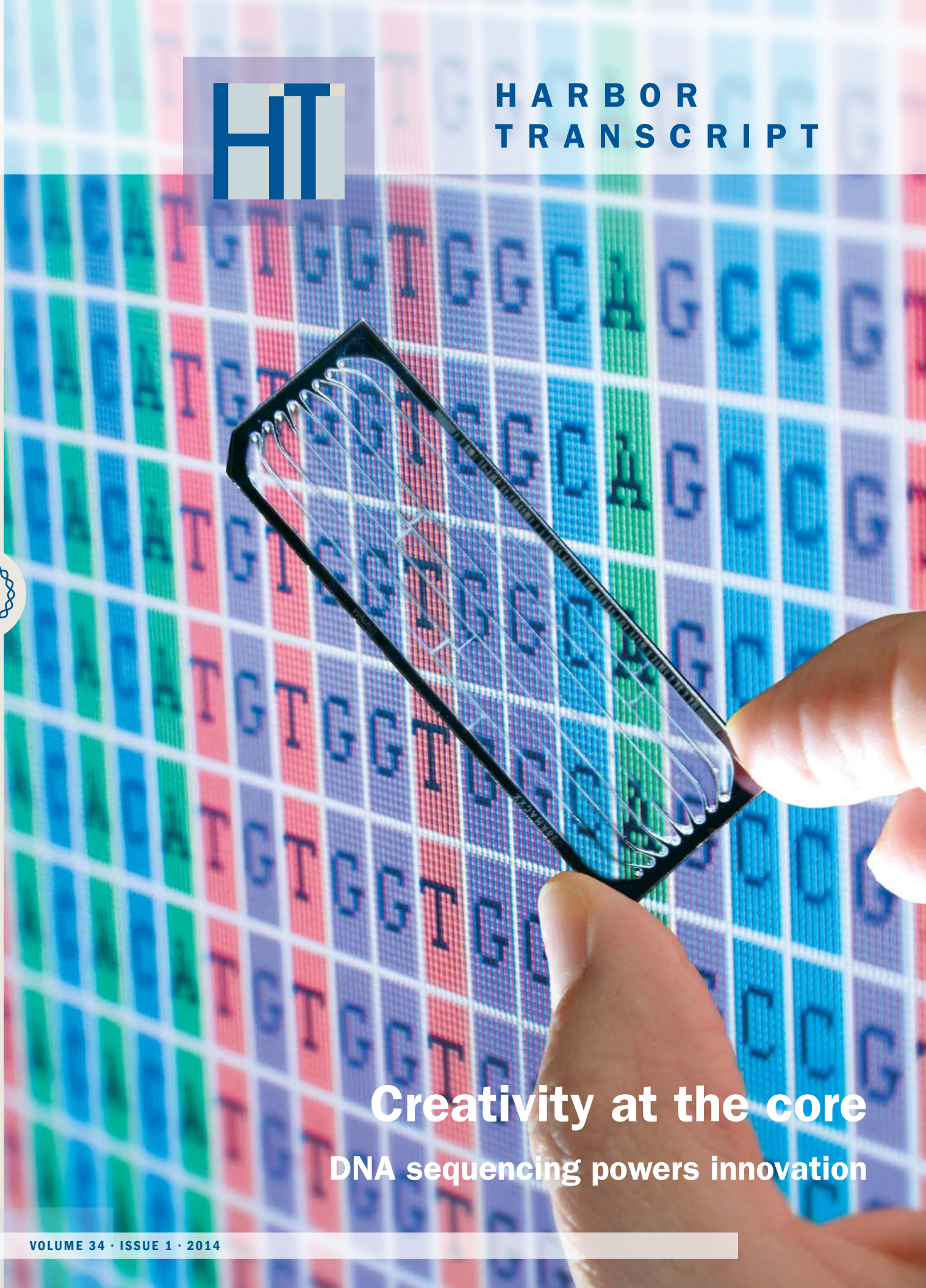
HARBOR TRANSCRIPT

Cold Spring Harbor Laboratory



Creativity at the core

DNA sequencing powers innovation

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Cold Spring Harbor Laboratory

PRESIDENT'S MESSAGE

Cold Spring Harbor Laboratory has been a central protagonist in the stories of genetics and genomics from their beginnings. Here, during the 1940s, the pioneers of molecular genetics annually met and learned from one another. In 1953, a very young James D. Watson made the first public presentation on the double helix in Bush Hall. In the late 1980s and early 1990s, Jim headed the Human Genome Project (HGP), the historic government-funded effort to map our genetic material.

Publication of the first draft of the human genome in 2001 heralded a new era in the biological sciences. According to a study by the Battelle Memorial Institute, our federal investment of $3.8 billion in the HGP through its completion in 2003 generated an estimated $796 billion in economic activity by 2011, much of it in the life sciences. That's $141 for every public dollar invested.

In ways you may not be aware of, genome sequencing, not just of human DNA, is impacting our personal health, how we think about feeding the world and how we address climate change by identifying alternative energy sources. But most profound has been the HGP's impact on the study of biology itself. In this issue, we take you inside the CSHL research enterprise to see how our scientists are harnessing the sequencing revolution to push the boundaries of biology.

Understanding genomes is central to CSHL. It is a theme that connects all of our research programs and influences what we are teaching in our wide-ranging biology education programs for middle and high school students. After you read the feature about genomics, notice how all of the other articles—about plant biologist Marja Timmermans; understanding autism; the work of the latest Ph.D.s from the Watson School of Biological Sciences; a family program of the DNA Learning Center; and a pictorial view of "One Experiment"—are connected by the conceptual thread of understanding genes and genomes.

At CSHL, genomics and genome sciences are not "siloed" research programs. They are an approach to discovery that drives research forward across fields. It also provides a great model for how wise public investment in basic research can yield benefits to science and society beyond our most optimistic expectations.

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On the cover:
A special kind of glass slide, known as a "flowcell," is where DNA sequencing happens. DNA is loaded into the vein-like channels etched in the slide's surface. The slide is then inserted into a sequencing machine where genetic information—encoded by the letters A, T, C, and G—is read.

Sequencing drives innovation

The Stanley Institute for Cognitive Genomics is home to 10 Next-Gen sequencing workhorses—HiSeq 2000 machines—with the capacity to sequence 3000 genomes a month.

It took 10 years and $2.7 billion to sequence the first human genome. Today, that same sequence can be read in a single week for one-millionth the cost, as little as $3000. Genome science has arrived.

What does this mean for biology? Because of astonishing advancements in sequencing technology, an entirely new field called genomics has come to life. It has enabled scientists to spell out the genomes of organisms across all branches of the tree of life, from yeast to plants to animals. The broad goal of this young field is to understand how changes in genetic information affect life. It is applied to single cells, individual organisms, even entire species. Genomics enables researchers to understand how breast tumors develop from an initial set of genetic errors. It also enables scientists to reach back through eons of time to understand how species evolve.

In labs around the world, sequencing technology has become a staple of basic and applied genomics research. At Cold Spring Harbor Laboratory, the same technology is also being used in creative and unconventional ways that reflect this institution's unique collaborative culture. The Laboratory has had the foresight to plan and build a cutting-edge genome-sequencing "core" facility that is available to every member of the faculty and, unlike most sequencing facilities elsewhere, is fully integrated into every facet of research on the campus.

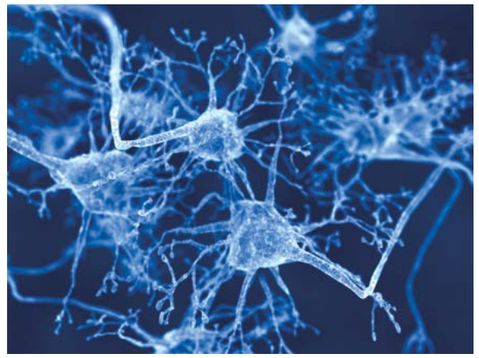
Moving beyond the straightforward compilation of genomic sequences—"read-outs" of the myriad individual DNA "letters" that make up individual genomes—CSHL scientists are developing new sequencing applications that have already generated impressive scientific results. They have found a gene that substantially increases tomato yields. They have identified a DNA element that pushes leukemia cells to keep growing. They are exploiting sequencing expertise to draw a complete circuit diagram of the mouse brain. And they are developing new diagnostics to improve cancer treatments that will cost as little as $10.

"Our core facility, the genome sequencing facility at Woodbury, has changed the way we collectively think about science," says Professor Richard McCombie, a pioneer of genomics and genome sequencing and director of the facility. "Because of our small size, we are flexible, cost-effective, and constantly at the forefront of technology. If somebody has an idea, we can jump on it—which provides a huge advantage to our researchers in this rapidly evolving scientific landscape."

The dawn of Next-Gen sequencing

Our genetic information is stored within our DNA, a long molecule that looks like a twisting ladder, whose rungs are made up of four chemicals called bases. The full human genome is composed of 3 billion bases, whose sequence, among other things, encodes some 20,000 genes. Roughly one out of every 1,000 bases varies from person to person. This means we differ from one another by about 3 million bases over the length of the genome. Inevitably, these single-base variations affect the way our genes are used (or "expressed," in the language of biologists). These differences are also what make each of us unique.

The first genomes were sequenced with technology that now seems quaint. In the early 1990s, researchers at CSHL worked in shifts around the clock to load DNA samples onto machines. At full capacity, they might be able to read 1–2 million bases a day, amounting to just 60 million bases a month. At that rate, it would have taken 50 years to read a full human genome.



The mouse brain contains more than 10 million neurons, and each makes nearly 1000 connections with its neighbors. CSHL Professor Tony Zador is developing a novel sequencing-based approach to build a full circuit map of the more than 10 billion neural connections in the brain.

3 billion
number of letters in the human genome

1.2 million
equivalent number of pages in a book

"Millions of bases may sound impressive," says McCombie, who also heads CSHL's Stanley Institute for Cognitive Genomics, "but today, the technology has advanced so that we are reading just shy of 10 *trillion* bases a month." That is the equivalent of more than 3,000 genomes.

The remarkable technology that makes this feat possible is known prosaically as Next Generation Sequencing (NGS, or "Next-Gen"). On average, it takes a little less than two weeks to sequence a single human genome, and each machine can process six genomes at once.

"We have 10 'Next-Gen' machines in our Woodbury core facility," says McCombie. Each one costs about $750,000, a steep price for individual researchers to pay on a lab-by-lab basis. "We pooled our resources—both in terms of finances and brain-power—so that our researchers have tremendous access to sequencing power, better than some of the largest institutions in the world."

"Our genomics investigators benefit from the large number of machines at their disposal, while scientists with smaller projects—even a single experiment—also have direct access to this technology, which is unusual." This, in turn, encourages creative applications of the technology, two of which are described below.

Using sequencing to map the brain

In one example, CSHL Professor Tony Zador, a neuroscientist, is using Next-Gen sequencing to determine how all of the neurons in the brain are connected. A map of the "connectome" will provide us with a better understanding of how the healthy brain works. But also, notes Zador, "we are beginning to understand that autism, schizophrenia and many other mental disorders are actually wiring problems in the brain. Projects like this one will help us pinpoint what goes wrong, and develop treatments for these illnesses."

The project, though simple in concept, is actually daunting in technological terms. There are more than 10 million

neurons in the mouse cortex and about 1000 synapses, or communications bridges, between *each* neuron. This means that scientists must map 10 billion connections to get a good idea of how the mouse brain is wired. "The conventional approach relies on microscopy to create this map," says Zador. But these projects are highly labor intensive and come at the tremendous cost of more than $10 million per year.

Zador has devised a method to genetically tag individual neurons with short sequences of DNA. This is akin to stamping a barcode on each one. In a trick of genetic engineering, Zador's team has found a way to drag the barcodes to the synapses where neighboring cells exchange messages. There, the barcodes are glued together. The fused DNA barcodes then can be isolated and sequenced with Next-Gen sequencing technology, just like any other DNA sample. Mathematical programs called algorithms enable Zador's team to make sense of the sequences in order to map connections not just between two cells but throughout the brain. If successful—it remains in the proof-of-concept stage—barcoding and Next-Gen sequencing may enable the team to generate a full-brain map for as little as $10,000 per brain, rather than tens or hundreds of millions.

$2.7 billion/10 years

to sequence the first human genome

$3000/2 weeks

to sequence six human genomes today

The CSHL sequencing facility is what turned this project into a reality. "I absolutely would not have thought of this project or been able to pursue it anywhere else," says Zador. "With all of the open discussion here at the Lab between people in different fields, I was able to see the power of sequencing and all it can do."

Sequencing single cells to diagnose cancer

CSHL scientists are also using Next-Gen sequencing to revolutionize cancer research. "Our goal has been to develop new kinds of diagnostics—to inform clinicians about the type of cancer cells they are treating so they can choose the best therapeutics," says Research Professor Jim Hicks, one of the lead scientists on the project.

A single tumor is made up of many different types of cells. Some may be susceptible to specific cancer treatments while others may be resistant to these same drugs. Doctors currently must biopsy a tumor in order to identify the aberrant cell types it harbors. Even then, pathology reports only provide a limited overview of the cancer.

Hicks and other members of Professor Mike Wigler's lab made a breakthrough when they developed methods to sequence cells one at a time. "We can extract DNA from blood samples or urine, so a minimally invasive blood test can replace a biopsy."

The next challenge has been to distinguish one type of cancer cell from another. Hicks and colleagues found that, in individual cancer cells, regions of the genome are duplicated or deleted. "These changes, called copy number variations, can be used to identify different types of cancer cells." This discovery means that it is no longer necessary to sequence the entire genome. Rather, Next-Gen sequencing is employed as a simple counting tool. "You can think of it as a small survey of the genome that lets us see where regions are deleted or duplicated," says Hicks. The advantage is that you can identify populations of cancer cells with a fraction of the sequencing data.

"The cheapest full genome sequence is at least a few thousand dollars, but we have devised a way to determine the origins of a cell for just $10," says Hicks, who hopes the work will lead to a marketable tumor diagnostic in the next few years.

Jaclyn Jansen

Help solve the puzzle

Meet Mike Ronemus, a research professor at CSHL. Mike is also a father—to a young boy with autism.

"For me," he says, "this is not just a job; it's personal."

Cold Spring Harbor Laboratory has one of the world's largest and most successful research programs in autism genetics. Ronemus and his colleagues, led by Professor Michael Wigler, are using Next-Gen sequencing to comprehensively search for DNA mutations in autistic children. The team has discovered that autistic children have a higher rate of spontaneous DNA mutations—"new" mutations that don't occur in either parent. This information is already changing how we think about autism spectrum disorders.

Ronemus filmed a Public Service Announcement with Cablevision to raise awareness and support for autism research at CSHL. "All this is possible because of contributions from private foundations and individuals. We are making a difference for children and families—including my own," he says. Check out the PSA online at cshl.edu/mike/

Jaclyn Jansen

Watson School 2014 Ph.D.s

Université Paul Sabatier - Toulouse III
Florence Gould Fellow

"Promoter evolution in *Drosophila*: non-coding transcription & transposon-driven innovation"

How "silent" areas of the genome can have a dramatic impact on how genes are expressed.

Università degli Studi di Pisa/ Scuola Normale Superiore
Goldberg-Lindsay Fellow

"A novel technology for the space-specific recovery of biological molecules"

Development of a laser-based technology to discover how gene expression varies at different locations within a cell.

University of Sydney
George A. and Marjorie H. Anderson Fellow
Genentech Foundation Fellow

"Characteristics of random monoallelic gene expression during embryonic stem cell differentiation"

A random feature of gene expression illuminates a surprising variability in how genes are used.

University of Guelph
William R. Miller Fellow
NSERC Scholar

"Meristem size and determinacy in maize"

How stem cell activity in plants can be exploited to increase food production.

Saint-Petersburg State Polytechnical University
Charles A. Dana Fellow

"Synaptic changes in the medial prefrontal cortex in susceptibility and resilience to stress"

How changes in neurons may underlie the behavior known as learned helplessness, a major symptom of depression.

Cornell University
Alfred D. Hershey Fellow

"Regulation of the auxin response by an ancient small RNA pathway"

How a small RNA pathway regulates the evolution of developmental programs in plants.

University of Warsaw
George A. and Marjorie H. Anderson Fellow

"Quantitative description of microRNA target site occupancy in mouse embryonic stem cells and derived cells of neuronal lineage"

Novel applications of sequencing technology to understand how small RNA pathways control gene expression in stem cells.

The University of New Mexico
National Science Foundation Graduate Research Fellow
Starr Centennial Fellow

"Investigating the roles of gene dosage and stem cell maintenance in the regulation of plant shoot and inflorescence architecture"

The genetic basis of the development of specialized reproductive branches that control fruit production.

Stony Brook University
Farish-Gerry Fellow
William Randolph Hearst Foundation Scholar

"A high throughput sequencing approach to mapping synaptic connectivity in the brain"

A new approach that uses DNA sequencing to map all of the neuronal connections in the mouse brain.

Stony Brook University
Farish-Gerry Fellow

"A computational framework for understanding decision confidence"

Determining the neural basis of decision making among the vast array of electrical signals in the animal brain.

University of Warsaw
George A. and Marjorie H. Anderson Fellow

"Unusual aspects of piRNA pathways in mice and flatworms"

Discovery of a protein that controls a small RNA pathway in reproductive cells to protect the genome from damage during the development of eggs and sperm.

B.S., 1964 Chemistry, California Institute of Technology

Ph.D., 1969 Biochemistry & Molecular Biology, Harvard University

Richard R. Burgess, Ph.D., James D. Watson Professor Emeritus of Oncology at the University of Wisconsin, received an honorary degree. An important figure in cancer, microbial and molecular research worldwide, Dr. Burgess has focused on RNA polymerase and the regulation of transcription. He has been the heart of the CSHL Course titled "Protein Purification & Characterization" since 1992. Dr. Burgess earned his Ph.D. at Harvard University under the tutelage of Dr. Watson.

One experiment

Humans, like most mammals, are made up of diploid cells. In the nucleus of each cell there are two copies of every gene, one inherited from each parent. Here, we see the nuclei (circled in white) of several diploid cells from a mouse: neural cells in an early stage of development.

Each nucleus contains one multi-colored dot, composed of separate red and green signals. The red indicates the DNA of a gene; the green, RNA. When the colors overlap, we know the gene is being activated—its code is being copied into an RNA message. But in each nucleus we also see an isolated red dot: it's the second copy of the same gene, and in these cells, it is not being copied into RNA. This is unusual. "You expect that when a gene is expressed, both copies are activated," notes Professor David L. Spector. Research by Mélanie Eckersley-Maslin, a graduate student in the Spector lab, demonstrates that in some cases, "a cell is perfectly fine expressing only one copy, or allele, of a gene, which we call monoallelic expression," Spector says. But why, and to what effect?

In one experiment, the CSHL investigators found that some monoallelically expressed genes encoded extra RNA, seemingly to make up for the loss of RNA resulting from the inactivity of their silent partner. This leads Spector to ask, "How does a cell 'know' what is the correct level of expression for every gene?" Random variations in expression may be advantageous in evolutionary terms, enabling cells to respond to a wider variety of conditions. But some variations could conceivably promote diseases like cancer—if, for example, a cell produces only half as much of a protein needed to suppress tumor formation. The lab's study of monoallelic expression is only just beginning.

Peter Tarr

RESEARCH PROFILE

Marja Timmermans

A feeling for the organism

CSHL Professor Marja Timmermans, a distinguished plant geneticist, is solving mysteries about essential mechanisms in plant development that have been perplexing people for hundreds of years. Her most recent research explains the developmental process in which emerging plant leaves "know" how to make distinct top and bottom surfaces. The work has implications in fields as wide ranging as agriculture and human health.

It took years of painstaking effort for Timmermans to unlock the secret of leaf polarity. The key discoveries, which include the identification of essential genes and surprising observations about signaling between cells, had to be assembled one by one, like pieces of a complicated jigsaw puzzle.

During her youth in the Netherlands, Timmermans was drawn to math and problems in logic. "It has always been puzzles that have really excited me," she says. This explains what would otherwise be a curious fact about her early life: upon finishing high school she aimed not to be a scientist but a police detective.

In 1987, while serving as a teaching assistant for the CSHL Plant Course, Timmermans met and was deeply impressed by Barbara McClintock, the CSHL scientist who had recently won the Nobel Prize for plant genetics work performed decades earlier. A new age was dawning, and discoveries made by McClintock—of "jumping genes," bits of DNA that hop around randomly in genomes, causing havoc—seemed to Timmermans all the more astonishing, given the primitive state of knowledge about genes when the discoveries were made.

This taught Timmermans a lesson, which she says is perfectly encapsulated in the title of a 1983 McClintock biography: *A Feeling for the Organism*. "Barbara really had a vision of the whole plant. From pigmentation patterns on the plant, she asked: what happens genetically and during development to make these patterns emerge in the form that we see?"

Timmermans went on to earn a Ph.D. in biochemistry at Rutgers University and set up her own lab at CSHL in 1998 as a CSHL Fellow. (She now directs the Fellows program.) A staff scientist beginning in 2001, Timmermans was a member of a pioneering cohort then using an approach called forward genetics to make new discoveries.

Every summer and winter, she and members of her lab, working in the Uplands Farm greenhouse, would plant 20,000–30,000 seeds in plastic flats. They were trying to find genes involved in setting up the top and bottom surfaces of leaves. "The 'forward' method was to plant massive numbers of seeds with a predisposition for mutation.

Normal maize leaf (left) is broad and blade-like. (White box: the meristem, its stem-cell reservoir.) In maize mutants identified by Timmermans, aberrant genes cause leaves to develop abnormally. In *leafbladeless1* (center) leaves are conical and thread-like; in *rolled* (right) they curl up.

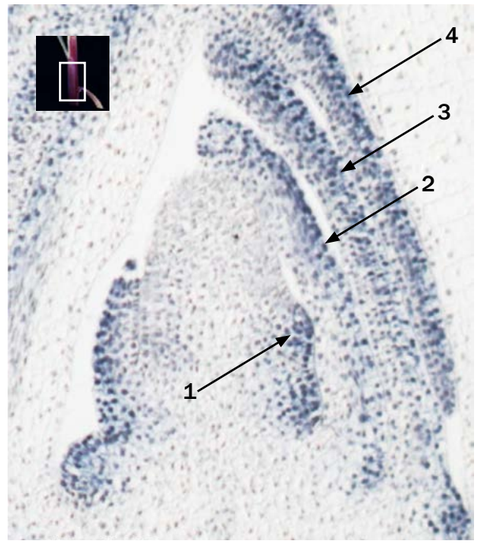
In screening for mutant seedlings—misshapen because of gene lesions—we screened for particular types of defects that we reasoned would be informative of leaf polarity."

A flat leaf is marvelously evolved to perform two related but highly distinct functions. The top side is a natural solar cell: it harnesses light from the sun to generate food for the plant. The leaf's bottom side serves as a place where gases enter and exit. To perform these dissimilar tasks, many leaves assume a flat, blade-like form.

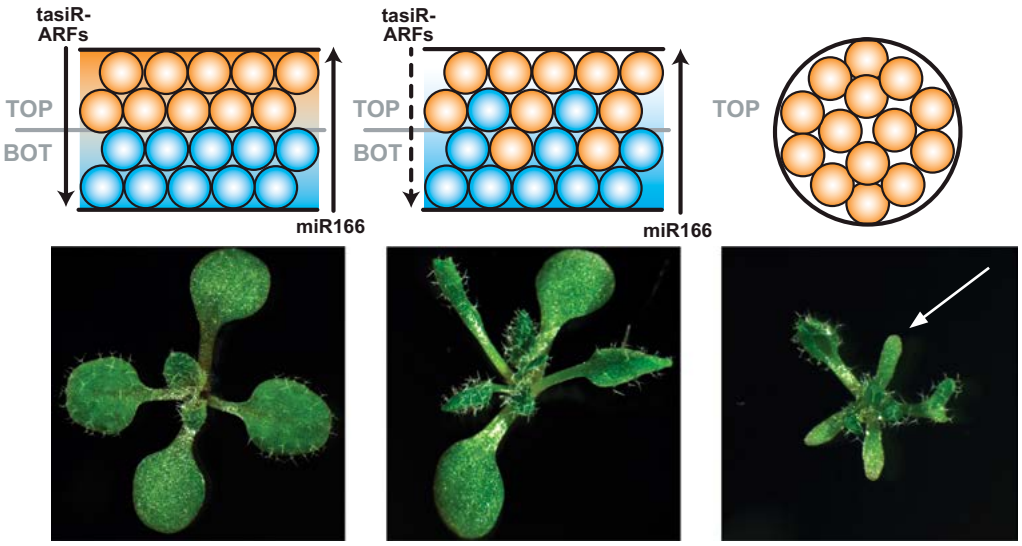
The first plant Timmermans worked on at CSHL "was this cute maize mutant called *leafbladeless1* (*lbl1*) that came out of one of our screens." Maize plants in which *lbl1* was mutated grew radial, thread-like leaves instead of the sturdy, broad-faced leaves of healthy maize plants. But why? What biological process was the gene a part of, and what went wrong when the gene was aberrant?

Over a period of years, forward genetics enabled Timmermans and her team to make an important discovery: the *lbl1* gene in a normal maize plant generates a small RNA molecule called tasiR-ARF, whose action is essential in establishing the identity of a developing leaf's top surface. When *lbl1* is mutated, as in the plants Timmermans screened in the greenhouse, the leaf is unable to develop in a blade-like form.

In the early years of the 2000s Timmermans used the same method to make a second discovery: a maize gene called *rolled* that when mutated caused emerging leaves to curl up. After tracing a series of developmental steps, Timmermans demonstrated that expression of this gene was ultimately tied to the generation of another essential small RNA—a microRNA called miR166. It proved to be indispensable in establishing the bottom surface of a blade-like leaf.



The stem-cell reservoir in maize (white box, insert). Emerging leaves begin as bumps (arrow 1); successive young leaves show characteristic top-bottom patterning: a small RNA called miR166 localizes to the bottom side of each (arrows 2–4), one of two key polarity signals.



How do leaf cells know whether to be 'top' (orange) or 'bottom' (blue)? Three images of mustard plant leaves, each corresponding with a drawing, above. In normal leaf development (left) two small RNAs assemble on the leaf to form opposing signal "gradients": tasiR-ARF is strongest at the top and miR166 strongest at the bottom. Center: "top" signal is weak, resulting in ill-defined boundary; leaf is curled. Right: "bottom" signal is missing; leaf, all "top," is radial.

Finding two genes essential for leaf polarity was a major coup. "It was a real surprise to discover that small RNAs played a central role," she says. But another major surprise was in store, in work that has come to fruition only in the last several years.

The geneticist as detective

Now using an approach called reverse genetics, her team begins with a gene of interest—like *lbl1* or *rolled*—and tries to pinpoint events "downstream" of its expression that go awry when the gene is mutated. "You start building these hierarchies of pathways, and you assemble a diagram: this gene…interacts with these other genes…which regulate this process, with these consequences…"

The challenge is to discover when, where and how during leaf development the expression of genes sets off a cascade of signaling events within leaf primordia. These are tiny bumps, incipient leaves just emerging from the stem-cell reservoir at the growing tips (meristems) of plants. Scientists have long known that signaling from the meristem somehow tells emerging leaves to form top and bottom sides. Forward genetics had enabled Timmermans to establish that small RNA molecules are involved; reverse genetics now led her to explain how these small RNAs give leaf cells positional information about what function to perform.

Unexpectedly, the small RNAs she had previously linked with leaf defects turned out to be mobile signals. By moving between cells, tasiR-ARF and miR166 form "concentration gradients" across the thickness of the emerging leaf [see illustration]. Based on where each cell sits along these gradients, it knows if it is going to be "top" or "bottom"—that is, whether it will develop into a light gatherer or gas exchanger.

Timmermans' discovery that microRNAs move from cell to cell to establish leaf polarity marked the first time that small RNAs native to an organism were shown to be capable of mobile signaling. "At first this was thought to be something quirky about plants," says Timmermans. Recently, though, small RNAs encapsulated within tiny spheres called vesicles have been shown to signal by traveling from cell to cell in mammals. Since signaling snafus are central in many human disease processes, work on mobile signaling by Timmermans and others "could very well" have future applications in the development of new human therapeutics, she says.

There is a more proximate application of the work in agriculture. Increases in maize yield have been obtained from optimizing the way leaves are positioned on the plant. Upright, as opposed to floppy, leaves enable farmers to increase yield by planting closer together. "One of the key traits that gives you upright leaves is the polarity pathway we have been working on," Timmermans notes. "We will want to tweak just a little bit—to make a little bit more 'top' than 'bottom'."

The detective in Timmermans is not ready to consider mobile signaling in leaves "case closed." "We still don't know how a particular cell actually senses the miRNA, measures its signal, and then knows how to react appropriately. It's a tremendously complicated puzzle!"

Peter Tarr

Got lactase?

Jennifer Galasso drew two halves of a circle on the big whiteboard, labeled “glucose” and “galactose.” Together, they form a big sugar molecule called lactose, said Galasso, a veteran instructor at the DNA Learning Center. *Where do we find lactose?* Half a dozen small hands shot into the air. “In milk!” crowed several of the young people, who had come with their parents for a *Saturday DNA!* lab about that curious human trait called lactose tolerance: the ability of some people to digest milk, even after infancy. *Some* people: only about 40% of adults continue to express a gene called *LCT* that directs cells of the small intestine to make lactase, an enzyme that cuts lactose into two digestible parts. About a dozen student-parent teams analyzed 4 “patient samples” of digestive fluid, which, after being exposed to milk—the step we see here—were tested for the presence of glucose. Got lactase? If so, there will be glucose in the test tube. Proof positive that a person can digest milk!

Peter Tarr

What are you doing Saturday? dnalc.org

Faculty & Friends

Islip Breast Cancer Coalition
Serving the People of Islip Township

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BREAST CANCER FOUNDATION
find a cure today

Joni Gladowsky
Breast Cancer Foundation
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WALK 97.5
Long Island's Best Variety

Glencove CARES

Hearts 2 Cancer

www.li2daywalk.org
LI2DAY
What's Raised Here Stays Here.

The Manhasset Women's Coalition Against Breast Cancer

Babylon Breast Cancer Coalition
For Life · For Hope · For Change · For the Future

Investigator update: Recognizing local partners who are supporting research in breast cancer at the Laboratory

Clinical Associate Professor Lora Weiselberg, M.D., of Hofstra North Shore-LIJ School of Medicine, teamed up with CSHL Professor Nick Tonks and Assistant Professor Mikala Egeblad to update local cancer advocacy and support groups on the current status of breast cancer treatment and next-generation therapeutic possibilities. The CSHL scientists are using their expertise in how enzymes influence communication signals in cells to address current obstacles to cancer treatment: metastasis and drug resistance. Advanced imaging technologies allow Dr. Egeblad to watch tumors grow *in vivo*. Dr. Tonks' understanding of proteins allows him to pursue new options for drugs targeting HER2-positive breast cancer tumors, a type that is particularly hard to treat.

Partners for the Future students are Intel semifinalists

Congressman Steve Israel (D-NY) joined CSHL in congratulating Long Island high school students who were this year's Intel Science Prize Semifinalists. Two of these 40 local semifinalists are currently participating in CSHL's Partners for the Future Program (PFF): Syosset High School seniors Priyanka Kumar and George Wang. A competitive program that selects participants based on a rigorous application process during their junior year, the PFF program invites participants to become members of one of CSHL's 52 investigator-led laboratories. Priyanka teamed up with cancer biologist Mikala Egeblad and George joined the lab of structural biologist and Howard Hughes Medical Institute Investigator Leemor Joshua-Tor.

Kepecs wins McKnight Award

Associate Professor Adam Kepecs, Ph.D., received the Memory and Cognitive Disorders Award from the McKnight Endowment Fund for Neuroscience for his work on the nucleus basalis (NB). NB is a vitally important but poorly understood part of the brain whose degeneration parallels the decline of cognitive functions in patients with Alzheimer's disease, Parkinson's dementia and age-related cognitive decline. Using state-of-the-art behavioral electrophysiology, quantitative psychophysics and optogenetics, Kepecs hopes to identify fundamental principles of neural circuit function to develop therapeutic treatments for cognitive diseases.

The McKnight Foundation
The McKnight Endowment Fund for Neuroscience

Stillman wins Tabor Research Award

CSHL President and Cancer Center Director Bruce Stillman, Ph.D., is an active researcher with many honors recognizing his pioneering work on DNA replication. He has now won the 2014 Herbert Tabor Research Award from the American Society for Biochemistry and Molecular Biology, and presented a lecture at its annual meeting. The award is given for excellence in biological chemistry and molecular biology and contributions to the community of scientists. Previous winners include Nobelist and CSHL alumnus Phillip A. Sharp (2009), whom CSHL recognized with a Double Helix Medal in 2006.

Herbert Tabor

Trustee Roy Zuckerberg endows cancer professorship

The first Roy J. Zuckerberg Lecture featured cancer physician and researcher Siddhartha Mukherjee, who won the 2011 Pulitzer Prize for *The Emperor of Maladies: A Biography of Cancer*. Introducing the event was David Tuveson, a fellow M.D./Ph.D. who runs CSHL's Cancer Therapeutic Initiative and who has been named the Roy J. Zuckerberg Professor of Cancer Research. "We're grateful for the support of trustees who understand the importance of a strong institutional endowment, a key factor in enabling innovative scientists like Dr. Tuveson to make progress in defeating the most deadly cancers," said CSHL President Bruce Stillman.

Dr. Tuveson was recently awarded the prestigious 2014 Jan Waldenstrom Medal by the Swedish Society of Oncology for outstanding contributions to cancer research. An expert in pancreatic cancer, Dr. Tuveson is also the Director of Research at the Lustgarten Foundation. At CSHL, the Lustgarten Foundation Cancer Research Laboratory is focused on early detection and finding a cure.

CURE PANCREATIC CANCER
• LUSTGARTEN FOUNDATION •

Mitra recognized by National Science Foundation and IEEE

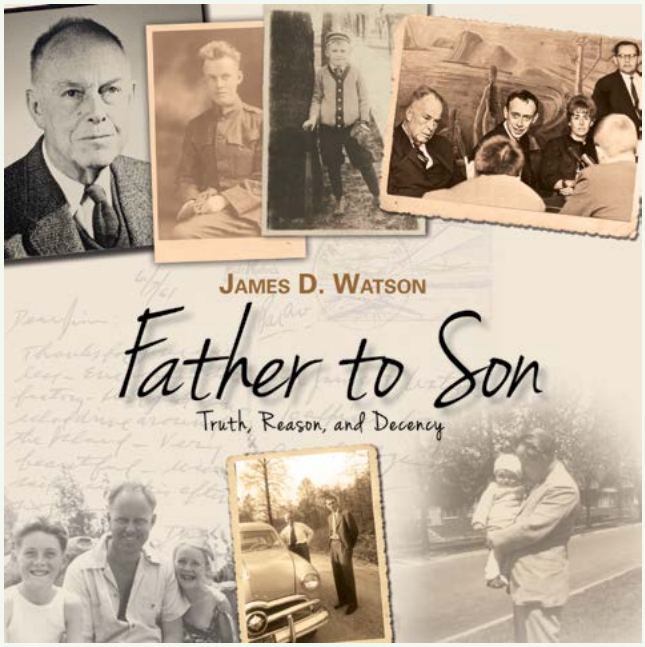
Partha Mitra, the Crick-Clay Professor of Biomathematics at CSHL, takes both neuroanatomical and theoretical approaches to understanding structural and functional properties of the mammalian brain. He received two recent honors for his multi-disciplinary approach: the George S. Axelby Outstanding Paper Award of the Control Systems Society of the Institute of Electrical and Electronics Engineers, and the INSPIRE grant, awarded by the National Science Foundation (NSF). Both recognize a common thread in Mitra's research: an attempt to bring concepts from physics and engineering to bear on outstanding problems pertaining to the difficulty of understanding the mammalian brain.

James D. Watson Award established by Hope Funds

The Hope Funds for Cancer Research has created the James D. Watson Award, with Nobel laureate and CSHL Chancellor Emeritus Dr. Watson being the first recipient. The award honors Watson for his unprecedented contributions to the field of biology and cancer research and will only be awarded to scientists who make comparable seminal discoveries. It was presented at the Metropolitan Museum of Art in New York City.

Father To Son, by James D. Watson published by CSHL Press

Always iconoclastic, in both science and literature, James D. Watson has written his autobiography in installments, beginning with the now classic *The Double Helix*, followed by *Genes, Girls, and Gamow* and *Avoid Boring People*. In *Father To Son*, the latest of his unsparing self-examinations, after a lifetime of exceptional accomplishments, Watson shows us that his heritage was remarkable and that "Most certainly I didn't emerge from nowhere!"



Father to Son was first intended as a small, privately published collection of the writings of his father. What emerged was a more complex story—the chronicles of an archetypical American family from before the Civil War to Vietnam.

"In this poignant book, Dr. Watson savors the evidence he finds about his father's life and values. It's a perfect book for anyone who has ever learned something from a father."

Walter Isaacson, author of Einstein: His Life and Universe *and* Steve Jobs

Jim Simons elected honorary trustee

The Board of Trustees elected James H. Simons an Honorary Trustee. Simons is founder of Renaissance Technologies and chairman of the Simons Foundation. “Jim Simons, who employed his mathematical genius to change the way the world thinks about financial markets, is now profoundly changing the world through philanthropy,” said CSHL President & CEO Bruce Stillman. Marilyn H. Simons, who serves as Vice-Chairman of CSHL’s Board of Trustees, leads the Simons Foundation, one of the nation’s leading private funders of basic scientific research. In recognition of their philanthropy, CSHL awarded the Double Helix Medal to Jim and Marilyn Simons in 2008.

CSHL Association

CSHL Association comprises some 1000 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, Annual Giving and Donor Relations, at 516.367.6886 or orzel@cshl.edu.