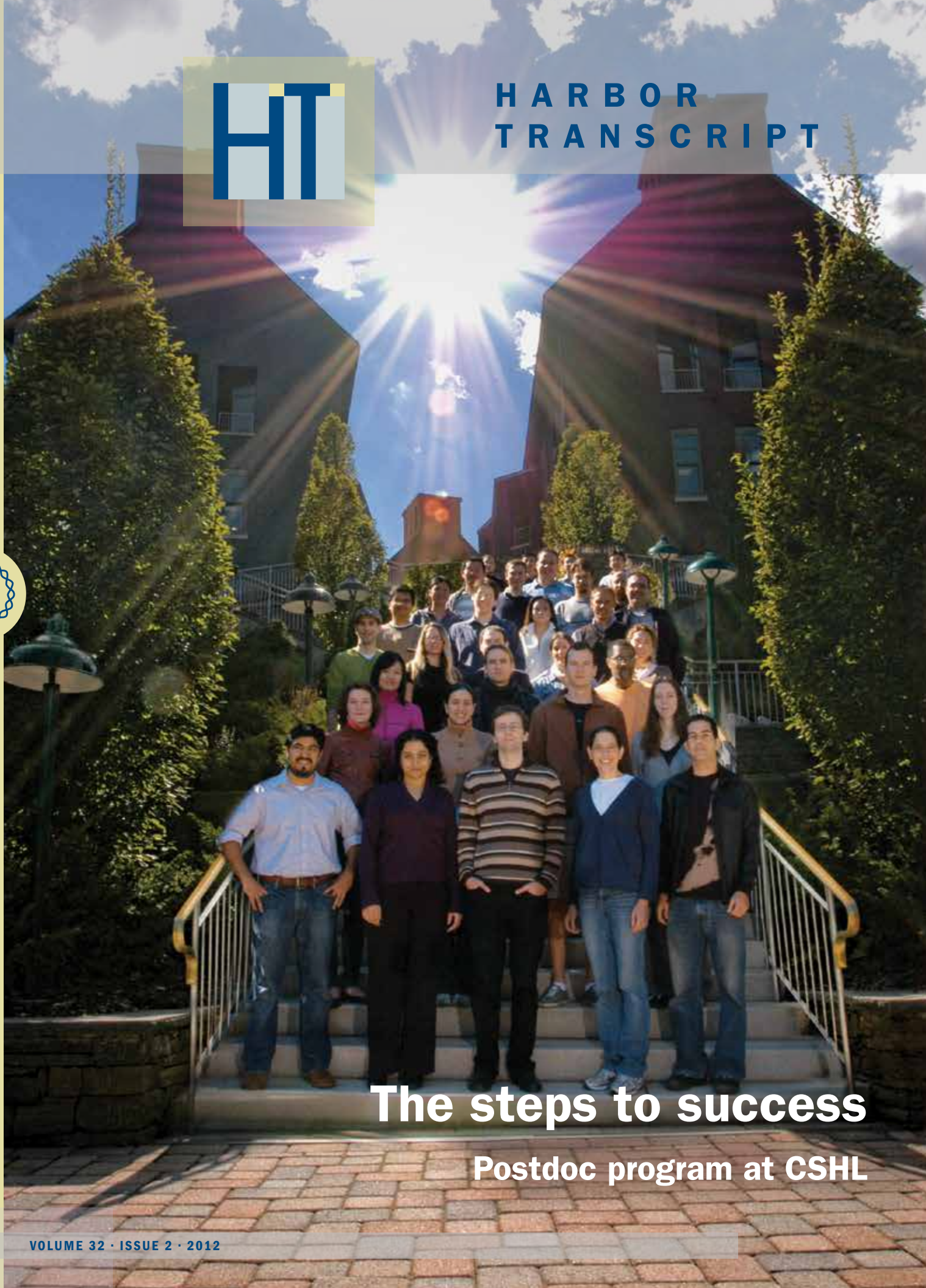
HARBOR TRANSCRIPT

Cold Spring Harbor Laboratory



The steps to success

Postdoc program at CSHL

VOLUME 32 · ISSUE 2 · 2012

PRESIDENT'S MESSAGE

The pages of this *Harbor Transcript* number more than usual and are filled with words and images of exceptional people. In an age in which technology seems to get all the applause, let's remember that it is people who make technology happen and people who use technologies to advance society.

The range of skills, experiences and interests of our nearly 1200 employees is remarkable and this magazine provides a good snapshot of that diversity. Read about our formidable contingent of postdoctoral trainees, who bring enthusiasm to our laboratories and invigorate campus life; and about our new cadre of Assistant Professors, with their fresh research perspectives. CSHL is living up to its reputation of being *the* place for the brightest young scientists to launch their careers.

Representative of our most senior investigators, Dr. Michael Wigler is a pioneer and innovator who has always been ahead of his time. You will read here about an idea that he considers "a game-changer" and promises to have a major impact on cancer diagnosis and therapy. These pages also introduce Dr. David Tuveson, a professor who brings a wealth of research and clinical experience to his new leadership roles as Deputy Director of the CSHL Cancer Center and the director of our new Lustgarten Foundation Pancreatic Cancer Research Laboratory.

The recent work of quantitative biologist Dr. Michael Schatz, chronicled here, is a wonderful example of how basic research, when harnessed to the needs of industry, can sometimes solve major problems in remarkably short order. And where will the next Schatz, Wigler or Tuveson come from? Perhaps a future CSHL investigator will be among the contestants in our DNA Learning Center's first-ever science competition, which, you'll learn, gave New York City kids access to DNA sequencing tools and set off a wave of exploration and experimentation across all five boroughs.

These scientists and educators are supported not only by laboratory students and staff, but by a community of benefactors and ambassadors who provide financial support. They help us expand our growing network of friends around the world. I extend my sincere thanks to all of the people who make this institution a leading force in biomedical research and education.

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On the cover:
A few of CSHL's 170 postdocs, pictured on the Hillside steps that lead literally to their labs and figuratively to their success in scientific careers.

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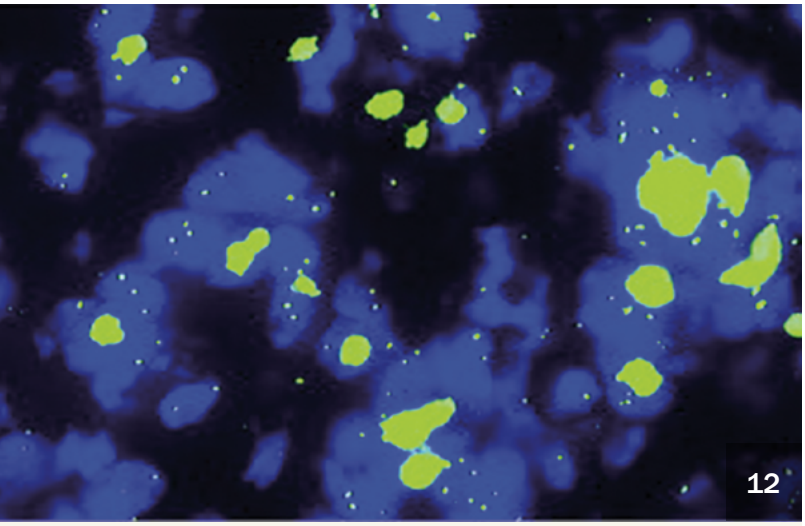
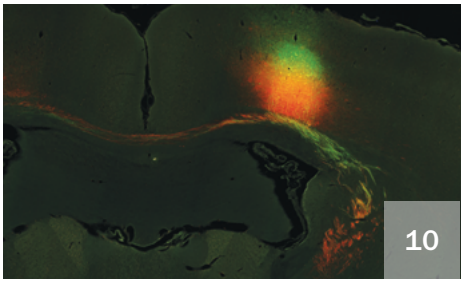


Dr. Michael Wigler discusses the promise of single-cell analysis, technology that will have a 'game-changing impact' in cancer



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FEATURES

FACULTY & FRIENDS

The steps to success

Postdoc program at CSHL

For a majority of those who spend long days in the lab, pull all-nighters, work through weekends, and willingly sacrifice vacations in the quest to earn a Ph.D. in the life sciences, life post Ph.D. is typically…not that different. As "postdocs," most will continue to live their lives at the lab bench, as night owls and weekend warriors for whom holidays and extreme weather events are mere glitches in a calendar crowded with experiments designed to address one of any number of challenging biomedical questions.

At any given time, CSHL is home to around a hundred and seventy postdocs. They arrive from 50 different countries, in their late '20s or early '30s, mostly by themselves but some with families, and work in one of CSHL's 54 labs from three to five years in pursuit of the same Holy Grail: a scientific breakthrough that will give them a chance to publish papers in the journals with the highest "impact factor," a measure of the journals' relative importance within a given research field.

By the time they are ready to leave, most will have accomplished this goal, which is one reason why CSHL is number one in the world in publishing papers in molecular biology and genetics that get cited most often, ranking above MIT, Rockefeller University and the Dana Farber Cancer Institute in this category. The postdocs know that authoring high-impact papers will add clout to their CVs, floating them to the top of the application pile in any science-related profession — particularly the coveted faculty positions in the rapidly shrinking pool of ivory tower jobs.

Most postdocs thus start planning for a post-CSHL career even as they begin their life on the campus. The track record of CSHL postdocs continuing on to successful careers is heartening, with most securing faculty appointments at top universities and research centers, and some advancing to such positions at CSHL itself — a prime example being President Bruce Stillman, who arrived here as a postdoc in 1979. But results of annual surveys conducted by the American Association for the Advancement of Science, the world's largest general scientific society, justify a certain level of anxiety. Unemployment following a postdoc stint has risen from 2% in 2010 to 10% in 2012, with only 20% of postdocs securing tenure-track faculty positions in 2012.

Navigating the job market was never this difficult for the postdoctoral community. In fact, in a distant 20th century period circa the '80s, some with Ph.D.s could skip the postdoc part and still land a faculty job. According to CSHL's Director of Research, Dr. David L. Spector, who comes from this era and acknowledges the challenges that postdocs face today, CSHL has all the ingredients needed to create a recipe for a successful postdoctoral experience.

"I tell postdocs to think of this experience as a unique time in their scientific lives when they are free of the responsibilities of managing a lab and competing for multiple grants," says Spector. "They are being given a chance to mix it up with the best minds in several research arenas. So the ball is in their court now. They just have to come up with great ideas, work really hard, and encounter a little luck in the mix."

Echoing his mentor's philosophy, Jan Bergmann, one of Spector's postdocs, is taking full advantage of the amenities that give CSHL's postdocs a huge edge over their peers elsewhere. "It's a combination of having easy access to the world's best scientific minds and the most advanced technology," says Bergmann, who is studying how recently discovered pieces of genetic material called long non-coding RNAs regulate the way DNA is packaged within the cell's nucleus and how this packaging changes as stem cells mature into different cell types.

Bergmann and his colleagues are benefitting immensely from CSHL's purchase of a cutting-edge microscopy system that tracks RNA-related events occurring within cellular nuclei in real time. "Most countries have just one of these machines; I'm fortunate to be able to use one that's a few minutes' walk from my lab," he says.

Another big technological draw for the postdocs is CSHL's Woodbury Genome Center, home to 16 high-throughput genome sequencing machines offering a broad array of genetic analysis applications that are constantly being innovated and improved upon in direct collaboration with the companies selling this technology.

In addition to the genomics hub, there are nine other "shared" scientific resource facilities that provide services ranging from breeding mice with a desired genetic profile to churning out indispensable reagents such as antibodies.

> "I tell postdocs to think of this experience as a unique time in their scientific lives when they are free of the responsibilities of managing a lab and competing for multiple grants."
>
> *David Spector, Ph.D.*

For postdocs running on a tight schedule and an even tighter budget, it's tremendously time-saving and cost-effective to have such facilities right on campus.

Access to the leading scientists in any given field is just as easy, often simply a matter of tracking someone down at lunch at one of the cafeterias or Blackford bar, where ideas for a new scientific front or a new technological approach are routinely hatched over coffee or other stimulating beverages. "There's a very strong culture of collaboration between scientists who work in different labs and across different disciplines," says Jonathan Ipsaro, a postdoc in structural biologist Leemor Joshua-Tor's group, who has joined forces with postdoc Astrid Haase in cancer biologist Greg Hannon's lab to make fundamental discoveries about the molecules that guide the phenomenon known as RNA silencing.

The lack of departments or other barriers "makes it easy for those who have trained in one discipline to learn new ones and think outside the box," says Santiago Jaramillo, a computational neuroscientist whose postdoctoral work in Tony Zador's lab is giving him "a solid foundation in experimental work in animals."

For postdoc Kate Creasey, who is unraveling mechanisms of epigenetics in plant biologist Rob Martienssen's lab, "it's not just the in-house expertise but the chance to meet and network with the scientific leaders who come to CSHL meetings from all over the world," that has been one of the highlights of her experience here. The CSHL meetings are crucial because this is where scientific discoveries are presented as breaking news. Hearing such information right away and not after six months when the discovery is published in a paper sometimes makes all the difference to a postdoc working in a competitive field.

Besides all these tangible factors, there's "an atmosphere of excellence where it's easy to be inspired," says former Spector lab postdoc Tom Misteli, who now heads the Cell Biology of Genomes group at the National Cancer Institute. "CSHL is a place where creativity is encouraged, as is the ability to take risks, think provocatively and venture outside the mainstream."

CSHL faculty takes an active role in promoting postdoctoral training with a view to improving their career prospects. Joshua-Tor, who until recently served as Dean of the Watson School of Biomedical Sciences, served on a National Institutes of Health task force that analyzed postdoc-related issues to frame a list of recommendations to improve postdocs' training and ability to forge a sustainable career. CSHL also provides its postdocs with other types of training, such as workshops on grant writing, navigating review panels and opportunities in non-academic sectors, to name a few. [see sidebar: "Preparing for the post-postdoc life"]

"Most of those who come here have already made headway into accomplishing many of the things they need in order to achieve their career goals," says Ipsaro. Wherever he and his peers land in the next stage in their careers, they will all do so with a nearly identical reflection on their CSHL experience. As Astrid Haase puts it, "the thought that we're pushing science further and doing things that make our work useful to the community for a long time makes the postdoc experience, with all its challenges, completely worthwhile."

Hema Bashyam

Preparing for the post-postdoc life

When a group of postdocs approached President Bruce Stillman in 2010 with requests for filling in some gaps in their experience at the Laboratory, he responded with a request of his own, asking them to organize into a formal group to pursue their agenda in a systematic way. The resulting Postdoc Liaison Committee has since changed the way postdocs are perceived by and interact with the rest of the CSHL community. "We're no longer the 'shadow' people," quips Kate Creasey, one of the leaders of the committee, whose job is "to ask the sorts of questions that will bring more transparency to the way postdoc-related issues are tackled and resolved." Some of the Committee's most successful activities include the initiation of a career development series in which faculty members educate postdocs on "real life" topics such as how to negotiate for a startup package after landing a faculty position or how to hire staff for a new lab.

For those keeping their options open for a non-academic life, the postdoc-run Bioscience Enterprise Club aims to provide opportunities to learn about non-traditional science careers, develop entrepreneurial skills and network with professionals in the biotech industry, clinical research, intellectual property law and tech transfer, consulting, science education, policy and administration.

Urban investigators

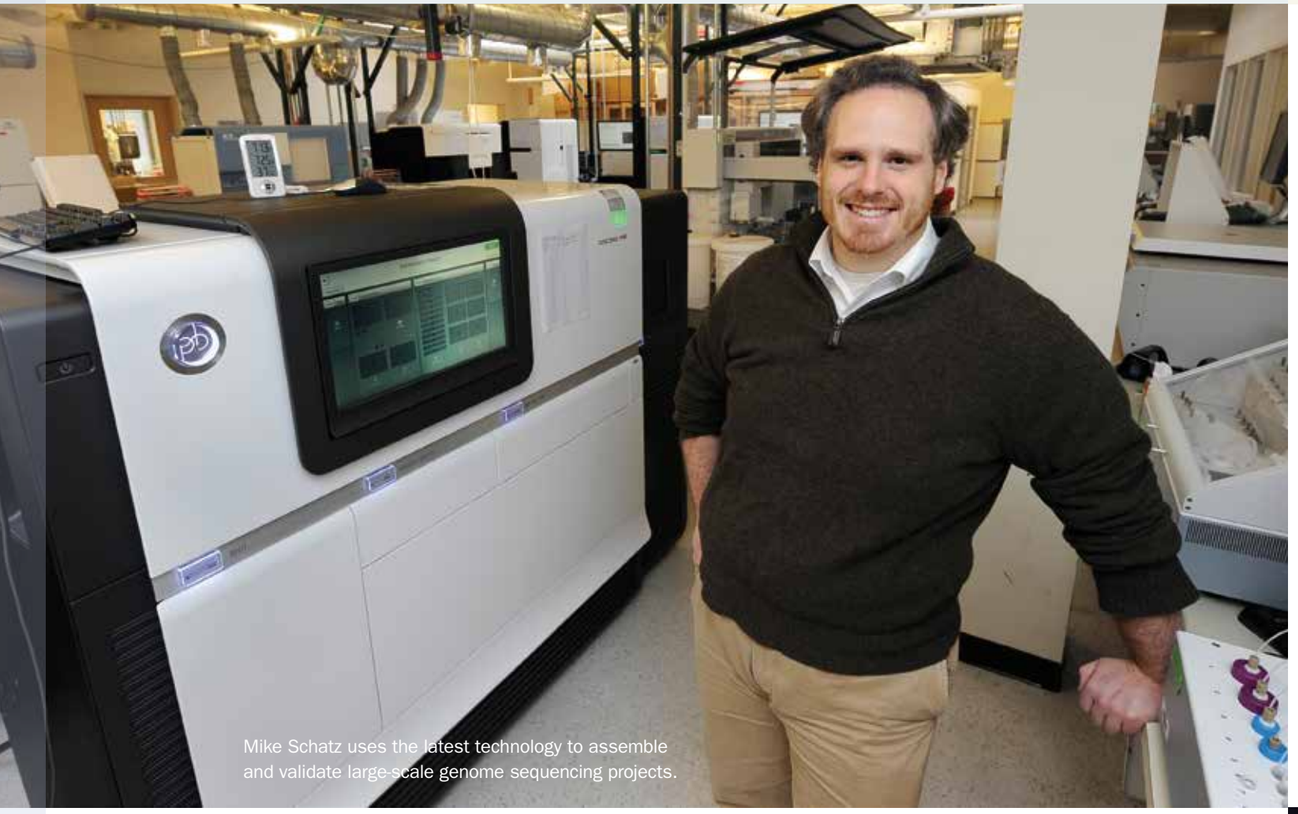
Bobby Glover, Marisa VanBrakle, and Mary Acheampong — grand prize winners in the citywide Urban Barcode Project organized by CSHL's DNA Learning Center (DNALC) — hail from Hostos-Lincoln Academy of Science in the Bronx. (They're seen here with their teacher, Allison Granberry.) The team's research project uncovered a surprising absence of the dietary supplement Ginkgo biloba in products claiming to contain the herb. As Alfred P. Sloan Foundation program manager and DNA barcoding pioneer Jesse Ausubel described, the student competitors selected a range of fascinating topics:

> *Projects about moss and lichens and birches and Christmas trees, about Biblical citrons and Mexican melons and Chinese pears, about fungal diversity in Central Park and mushrooms for sale in Chinatown. About cod and catfish and crab and small killifish…About salamanders and mosquitoes and nematodes and bedbugs, about Jamaica Bay and about weeds and tree boxes and about ants of the South Bronx. About the content of pet food, and animal and plant origins of adhesives and glues in artwork.*

This first-ever NYC barcoding project succeeded in attracting students — over 300 students in all — into the laboratory as collaborators and allowing an unprecedented number of science students to work as teams in many locations simultaneously. DNA barcoding integrates different methods of scientific investigation — from *in vivo* observations to *in vitro* biochemistry to *in silico* bioinformatics. DNALC Executive Director David Micklos hopes that "this core New York project provides a well-oiled infrastructure on which to build additional initiatives in other locations in the U.S. and abroad."

Dagnia Zeidlickis

Genome sequencing's big fix



Mike Schatz uses the latest technology to assemble and validate large-scale genome sequencing projects.

The age of individual genome sequencing is almost upon us. There are already companies, like 23andMe, whose sole business is to sequence your genome and inform you of potential disease risk factors in your DNA. But to truly make this a globally accessible technology there are still some hurdles to overcome.

CSHL Assistant Professor Michael Schatz has set out to improve genome sequencing by removing some of those hurdles. One important concern is the accuracy of the sequences being produced. Just as your eye might mistake a letter or word when reading, sequencing machines sometimes misread a unit of DNA, known as a base pair, in a genome sequence. Schatz's group made a big splash earlier this year, when it achieved a breakthrough in just this area.

Sequencing technology's rapid advance

Sequencing technology has come extremely far in very little time. It took $3 billion and years of work to sequence the first human genome, which was finished in the year 2000. Now, the cost of sequencing the entire human genome is down to about $3000 and can be completed in a matter of days. This is currently done using a technique known as second-generation sequencing.

It was the advent of second-generation sequencing technology, or "2nd-gen" as it is called, that rapidly advanced the field. Small DNA molecules — extremely short pieces of the full genome — are copied many times over. These fragments are then analyzed all at once, generating lots of short sequences, also known as "reads" (i.e., genome segments read by a sequencer). Doing it this way ensures high accuracy in the DNA sequence output.

The downside, however, is the length of those short reads, which are typically between 100 and 200 DNA base-pairs long. The human genome is huge, about 3 billion base pairs. "It's like sifting through billions of tiny jigsaw pieces when the overall picture is of a blue sky," says Schatz, "and this becomes a real limitation when you are trying to see the big picture."

Third-generation sequencing, a new technology released for beta testing about two years ago by Pacific Biosciences, offers significantly longer reads. It manages this by sequencing one comparatively much longer DNA molecule at a time. "The very special thing about 3rd-gen sequencing is you can generate these very long reads," says Schatz. Indeed, while they typically range in the thousands of base pairs, the longest read Schatz has seen from a 3rd-gen machine is tens of thousands of base pairs in length.

Comparatively puny, the 100 to 200 base pair 2nd-gen reads are far shorter than the average length of a human gene, which is about 3000 base pairs. The major advantage of long reads is that they often cover much more than the sequence of a single gene, making it easier to resolve the sequence of many genes in a row. This allows researchers to more accurately assemble the full genome sequence.

But even with this improved method there is a crucial trade-off. Third-generation sequencing is considerably less accurate than its predecessor. The error rate can be as high as 15%, meaning roughly 1 in 6 base pairs will be read incorrectly. So while in theory those long reads would be a major leap forward for genome assembly, Schatz notes that "the quality is so low that you can't directly use those reads for a lot of things you want to do."

Schatz and McCombie among the vast computing servers that power their research.

Best of both worlds

Motivating Schatz to find a fix for these errors was the goal of providing highly accurate versions of complete genomes. Such a solution would be extremely relevant across multiple disciplines, e.g., basic research and applied medicine, as well as for biotechnology companies involved in making sequencers.

As a computer scientist, Schatz gravitated toward a software-based solution. He and his collaborators, including CSHL professor W. Richard McCombie, Ph.D., a sequencing pioneer, came up with a hybrid approach that fuses the best aspects of both 2nd- and 3rd-gen sequencing.

"We wrote a software program that takes the short, accurate reads from 2nd-gen sequencing and uses them to polish the long reads generated by 3rd-gen technology," Schatz explains. The software scrubs out the mistakes, reducing them to a paltry rate of about 1 error in 100 base pairs.

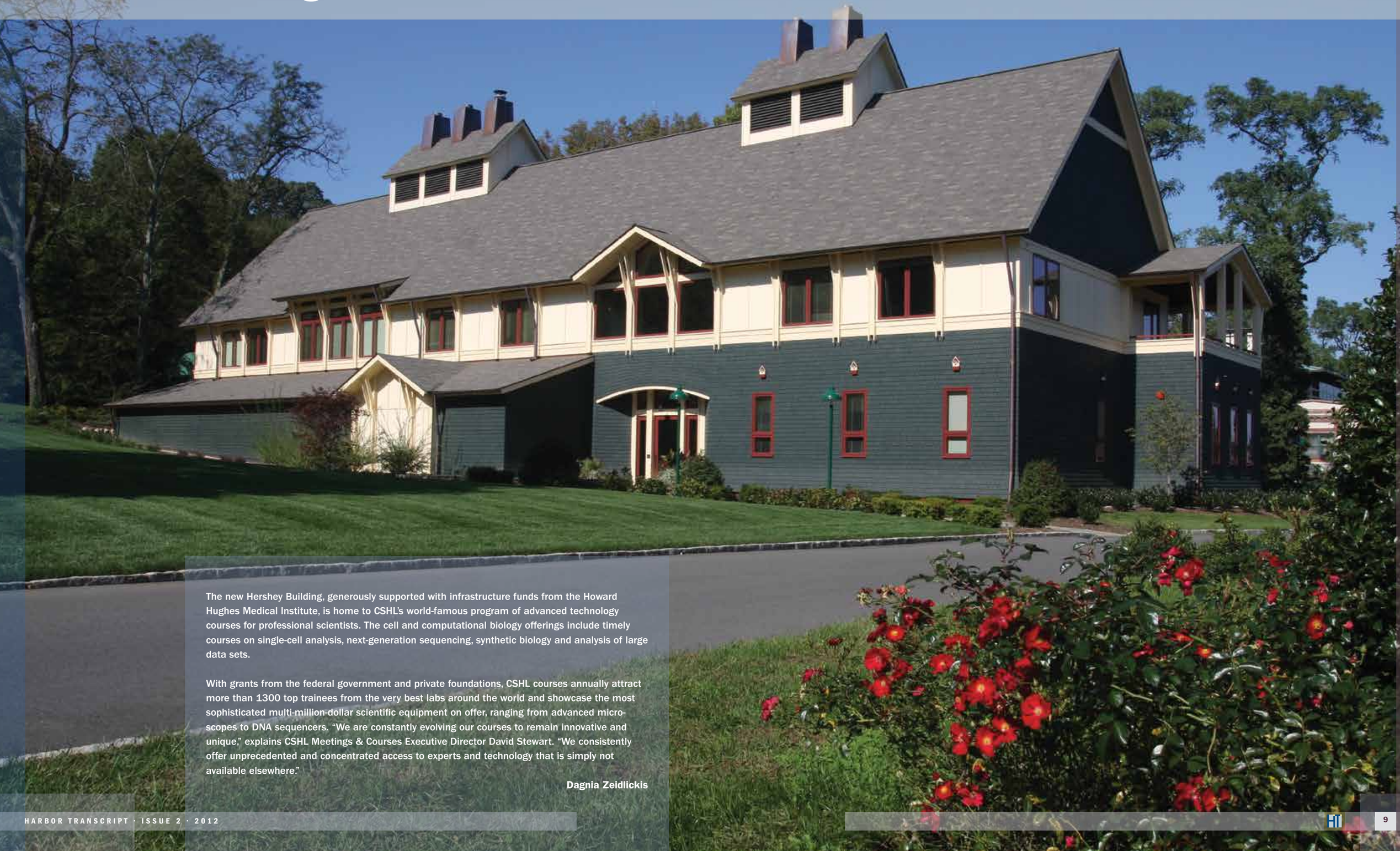
Generating sequences is relatively easy; it is assembling them into the full genome sequence that is the hard part. This is made much harder if there are errors in the sequence. So while the software solution Schatz and his colleagues developed means sequencing a sample using both 2nd-gen and 3rd-gen methods, they maintain it is worth the effort. There is a huge benefit, they say, in the amount of time and money saved when assembling the full genome.

After publishing their work in a *Nature Biotechnology* paper earlier this year, Schatz and his team are now eager to apply their software fix to new biological and medical research problems. His group is already engaged in collaborative study with CSHL geneticist Mike Wigler to look for disease markers in the genomes of children with autism.

This research is possible only because of advances in sequencing technology, including Schatz's own software solution. Using these new methods Schatz and Wigler can sequence, assemble, then study the genomes of thousands of children with autism for their project. This gives them a much greater chance of finding something significant.

Edward Brydon

Training for the future now



The new Hershey Building, generously supported with infrastructure funds from the Howard Hughes Medical Institute, is home to CSHL's world-famous program of advanced technology courses for professional scientists. The cell and computational biology offerings include timely courses on single-cell analysis, next-generation sequencing, synthetic biology and analysis of large data sets.

With grants from the federal government and private foundations, CSHL courses annually attract more than 1300 top trainees from the very best labs around the world and showcase the most sophisticated multi-million-dollar scientific equipment on offer, ranging from advanced microscopes to DNA sequencers. "We are constantly evolving our courses to remain innovative and unique," explains CSHL Meetings & Courses Executive Director David Stewart. "We consistently offer unprecedented and concentrated access to experts and technology that is simply not available elsewhere."

Dagnia Zeidlickis

One experiment

Via a Web-based portal built by his lab team — www.mouse.brainarchitecture.org — CSHL Professor Partha Mitra takes us on a journey to the final frontier of human biology, the brain. His team is fast closing in on their goal of providing the first whole-brain circuit map of the mouse. The rationale: to generate a reference wiring diagram to identify circuit alterations in neurological disorders, and to understand brain evolution by comparing wiring diagrams across species.

Using four neural tracers injected sequentially at 250 brain locations in mice of identical age and sex, the team enables us to follow branching projections from myriad neurons over the full volume of brainspace. Each injection can be thought of as one experiment. This image takes us on one partial journey of many thousands as the full circuit is compiled, mouse by mouse, each brain imaged robotically in 500 cross-sections, each section 1/50 mm wide.

This journey begins with injections of red- and green-labeled tracers at different depths in the left motor cortex. The injection appears on the right, as we look into the brain from the perspective of the mouse's nose. Fibers project from the motor cortex in two main bundles. To our left, axons shoot across the corpus callosum to the opposite hemisphere, presumably to help coordinate activity of the two sides. To our right and down, fibers project into the striatum on their way to connection with the thalamus, brain stem and spinal cord. [follow their path in HT iPad app] The human analogs of these fibers are thought to control our hands — neurons on the left side controlling the right hand. It boggles the mind to consider the myriad functions that will be traceable once the full-brain circuit map is completed. Then too we will have a basis for a wholly novel perspective on brain structure and dysfunction in autism, schizophrenia and other major disorders.

Peter Tarr

RESEARCH PROFILE

Michael Wigler

A game-changing technology in cancer

In recent months, Professor Michael Wigler has been writing and speaking publicly about what may be the Next Big Thing in biology. Called single-cell analysis, it's a new way of learning about what's going on inside cells. When it is more fully developed in the years just ahead, it will provide a clearer view than we've ever had of how cells work and what goes wrong when they're not working right — for instance, in cells of a cancerous tumor or a diseased heart or a deeply depressed brain.

Wigler, a geneticist who is the American Cancer Society Research Professor at Cold Spring Harbor Laboratory, considers single-cell analysis "an amazing, transformative technology — a total game changer." He thinks it is very likely to bring near-term benefits for human health, at first in the area of diagnostics, and over time in the way serious illnesses are treated. We focus in this article on cancer.

"Single-cell analysis" actually refers to several emerging technologies and methods. What they have in common is their object: living cells, considered one at a time. Looking in various ways at 100 to 1000 cells sifted from a single sample of tissue, blood or urine will provide a snapshot of what genes are being expressed at a moment in time, or what proteins are present in the cell's cytoplasm.

These things are possible to determine today at comparatively low resolution, using painstaking and costly methods. In addition to getting much more detailed results, what's new about single-cell analysis is being able to consider the varied properties of a single cell — which are in flux over time, in ways we don't yet understand — in the context of knowing that cell's full genome sequence. Single-cell genomes have not been technically possible to ascertain until now. [see sidebar: "Single-cell analysis: in brief"]

The entire package of single-cell data will enable us to understand in unprecedented ways how cells differ subtly from one another. It's information that opens new windows on the biology of normal cells as well as on human pathology.

Techniques usually employed in research and commercial biomedical testing yield results that represent average readings of the properties of *millions* of cells in a given sample. You can learn important things from averages. But as Mike Wigler observes, processes pertinent to illness "are often happening in *rare* cells within a large population. So when you analyze a whole population at once — say, the mass of cells removed in a tumor biopsy — you miss these things."

Wigler expects that single-cell techniques will transform cancer diagnosis and treatment, making it possible not only to detect cancer cells much earlier, in some cases even before a detectable tumor forms, but also to know how best to treat tumors that have formed and accurately predict how they will respond to therapies.

An opinion to be taken seriously

"One of my dreams," Wigler says, "is that any of us will be able to walk into a doctor's office, he'll be able to draw blood, and there'll be a fairly routine and inexpensive test that tells you within a few hours if you have cancer somewhere, and where in your body it is."

This dream should not take long in becoming reality, Wigler predicts. The technologies for such a test are now being developed at CSHL and elsewhere and should be available within 2 to 5 years. While this is only an estimate, Wigler's is an opinion to be taken seriously. He is a scientist of remarkable and diverse accomplishment, a consistent innovator whose deep thinking on big problems and long list of seminal insights has earned him the respect of his peers and a reputation for seeing things that other people fail to perceive. One recent example is his 2007 "unified theory" of autism's genetic causation, which surprised many by predicting an important role for spontaneously occurring, non-inherited mutations. This and other aspects of the theory are so far being confirmed in research at CSHL and other institutions.

A math major at Princeton who after graduation began training at Rutgers and later Columbia to be an M.D., Wigler was recognized by his mentors to have a gift for abstract thinking. Leaving his medical studies behind, he found his niche while earning a Ph.D. in microbiology at Columbia in the mid-1970s in the lab of Dr. I. Bernard Weinstein.

Wigler's first big ideas, incubated in the Weinstein lab, were whoppers: a pioneering method (called transfection) of transferring DNA between animal cells; and a method called co-amplification that involves getting one gene to associate with another, making it possible to mark them for subsequent selection. Completed together with Richard Axel and Saul Silverstein, the latter method, whose potential in drug development Axel appreciated, famously earned Wigler's alma mater Columbia a billion dollars in patent revenues, and instant respect for the young microbiologist.

When he joined the CSHL faculty in 1978, Wigler was focused on using the techniques he had developed at Columbia to study cancer. His group was first to isolate a mutant gene from a human cancer that when placed in a "normal" cell could cause that cell to undergo cancerous transformation. The mutant gene was *H-ras*, and its co-discovery in 1981 by Wigler and an independent team at MIT helped usher in a historic period of discovery in cancer genetics.

Wigler's discovery and others after it were dependent on the tools he developed at Columbia. It marked the beginning of a career pattern. To this day, Wigler thinks of himself as a tool-builder.

Isolating 'signal' from 'noise'

In the 1990s as the age of genome sequencing dawned, Wigler and colleagues, including Nikolai Lisitsyn and Rob Lucito, invented tools with which to compare two genomes. The first version of this idea, called representational difference analysis or RDA, was the answer to a problem that cancer geneticists wanted to solve but couldn't, for lack of a tool. Precious insights awaited if one could reliably compare, for instance, the genome in cells sampled from a patient's breast cancer with genomes in that patient's healthy tissue. How, precisely, did the "cancer" genome differ?

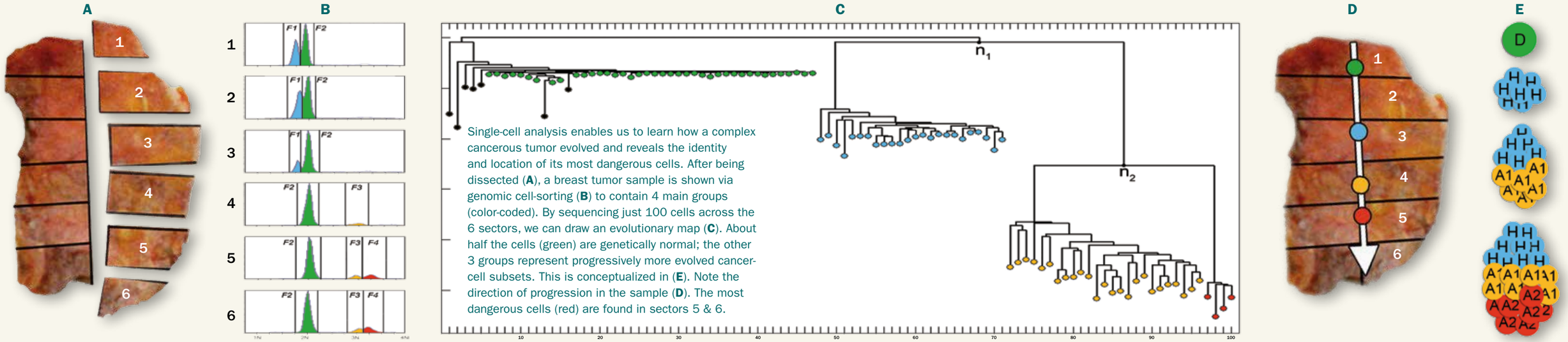
"I used to call this the fundamental problem of biology," Wigler says, referring to the problem of genomic comparison. It involves a challenge that recurs throughout his work: how to isolate a meaningful signal that is

Single-cell analysis: in brief

We have been sequencing whole genomes for over a decade, but not until recently has it been possible to think of getting a full genome sequence from the DNA contained in a single human cell. Current methods piece together a single genome by assembling, roughly, a billion bits of DNA derived from a million cells. The resulting genome therefore represents a "consensus version" of the DNA sequences found across the entire population of cells that contributed to the assembly.

But what if you wanted to know how the genome of a single cell — say, a cancer cell in a particular part of a prostate tumor — compared with another cell in the tumor? Or in a metastatic outpost of the primary cancer? It was not possible to make such a comparison of single cells until the Wigler lab figured out how to capture enough of a genome from the DNA in one cancer cell to read copy number variations and thus get a meaningful picture of the mutations in that cell. In refinements of this approach, Wigler's team has classified different clonal subpopulations of cancer cells in tumors and is now making the procedures much more cost-effective — a condition for clinical utility.

Single-cell analysis, whether in cancer or in other applications, brings other technologies into play, involving, for instance, the precise measurement of RNA messages in the nucleus at a given moment in time — an index of what genes are being expressed; or fine-grained accounting of the many types of proteins present in the cytoplasm of a single cell. It is really as an ensemble of technologies that single-cell analysis becomes extremely powerful.



Single-cell analysis enables us to learn how a complex cancerous tumor evolved and reveals the identity and location of its most dangerous cells. After being dissected (**A**), a breast tumor sample is shown via genomic cell-sorting (**B**) to contain 4 main groups (color-coded). By sequencing just 100 cells across the 6 sectors, we can draw an evolutionary map (**C**). About half the cells (green) are genetically normal; the other 3 groups represent progressively more evolved cancer-cell subsets. This is conceptualized in (**E**). Note the direction of progression in the sample (**D**). The most dangerous cells (red) are found in sectors 5 & 6.

embedded in an ocean of distracting noise. In considering two highly complex and nearly identical objects — like two genomes — how could one isolate what's different about them, while setting aside all the things about them that aren't important in the context of answering a specific question?

RDA and a related technology Wigler's team later developed called ROMA, which greatly increased RDA's power by adapting it to microarray technology, made such comparisons possible. This major advance and others facilitated studies that greatly changed our picture of many diseases, including cancer. We learned that cancer is not a single disease but many, with a bewildering array of genomic signatures.

Analyzing heterogeneity within tumors

"Cancer genomes have lots of mutations, and in the past we have explored these by extracting DNA, comparing it to normal DNA of the person, and from that getting an 'inventory' of [genetic] problems," says Wigler. "As far back as 2002, though, I've had the idea of trying to find out about cancer by examining the genome in *single cells* from a tumor."

If there were no rhyme or reason to tumors — if they multiplied chaotically, and utterly unpredictably, as many once believed — the advance represented by single-cell analysis would not be so useful in cancer. "There was no reason to assume that cancers were genetically heterogeneous; but the advance represented by single-cell sequencing analysis showed otherwise," explains Wigler.

His team has been the first to figure out how to determine gene copy number in individual human cancer cells, a critical first step in getting a useful genome readout from single cells. There's an important backstory here: in the early part of the 2000s, Wigler and colleagues made a landmark discovery: We all harbor gene copy number variations (CNVs), meaning that instead of the two versions of each gene that we're presumed to possess (one copy inherited from each parent), the average person has several dozen spots along their chromosomes where there is either too much or too little DNA, relative to the "reference" human genome. Most CNVs are innocuous.

In cancer, Wigler and others have observed recurring chromosome "breakpoints" marking places where small or large segments of DNA are either amplified or missing. These are good places in the genome to look for oncogenes and tumor-suppressor genes. In cancer cells one might see many extra copies of an oncogene like *K-ras* or Myc, or the deletion of one or both copies of a critical tumor suppressor gene like *PTEN*.

"Thanks to the bravery of a postdoctoral student in our lab, Nicholas Navin," says Wigler, and the collaboration of Wigler's longtime research colleague Jim Hicks, a CSHL Research Professor, his lab has devised a protocol for sifting massive numbers of cells from a tissue sample to find a much smaller number likely to bear the genomic marks of cancer — and to then sequence their genomes, cell by cell, using high-throughput technologies.

In 2009, Navin (now on the faculty of M.D. Anderson Cancer Center), Hicks and Wigler demonstrated that gene copy number data on a small number of single cells sampled from different locations in several breast tumors accurately reflected the irregular genomes of the corresponding primary cancers, replete with chromosomal breakpoints and gene copy number variations.

Many of the breast cancer samples scrutinized by the team consisted of several distinct subpopulations of genetically aberrant cells. The team can ferret out and individually characterize each subpopulation. In 2011 they used single-cell sequencing to show that many breast tumors evolve "clonally," in a few punctuated, staccato-like bursts — as opposed to very gradually, bit by irregular genomic bit, as some have supposed. [see illustrations, above]

A clone is a group of genetically identical cells that share a common ancestor. From a single clonal population of aberrant cells, cancers are revealed in single-cell sequencing to advance — and thus enhance their chances of survival — by capitalizing on the process of mutation, which is always occurring, but at a quickened pace in cancer as tumor cells seek new resources to support their continued growth and expansion.

Cells that manage to mutate so as to circumvent threats to their survival — the body's immune cells or poisonous anticancer drugs — gain a survival advantage. Such cells can form the basis of a newly resistant clonal subpopulation within the tumor and seed continued growth.

By exposing clonal subpopulations and inferring their mutational history, Wigler and colleagues have devised a new way to gauge prognosis, while laying bare the specific genetic abnormalities that drive the cancer forward. This can inform treatment decisions and the search for new treatment targets.

Mike Wigler is enthusiastic about what single-cell analysis will be able to do, but he is also emphatic about what it cannot be expected to do. "These methods are, as I said, transformative. But not because they provide answers; rather because they provide a tool to answer questions that couldn't get asked before."

Peter Tarr

Six new faculty

CSHL continues its historic commitment to attracting and promoting world-class research faculty. According to Director of Research David L. Spector, who heads the institution's recruitment efforts, "in the last year, we have strategically invested in research faculty who are at the forefront of cancer therapeutics, genetics and genomics of human disease, computational biology and bioinformatics. We look forward to the significant impact that we know these exceptional scientists will have in shaping the future of biomedical research."

David Tuveson, M.D., Ph.D.

Professor
Deputy Director, CSHL Cancer Center

Dr. Tuveson obtained a bachelor's degree in chemistry at MIT, followed by M.D. and Ph.D. degrees at Johns Hopkins. After a faculty position at the University of Pennsylvania, he moved to the University of Cambridge to develop preclinical and clinical therapeutic strategies. CSHL recruited Dr. Tuveson to direct the Cancer Therapeutics Initiative (CTI) and serve as Director of Research for the Lustgarten Foundation. He continues to practice medical oncology with an adjunct appointment at Memorial Sloan-Kettering Cancer Center.

The Tuveson laboratory investigates fundamental aspects of cancer biology and applies this knowledge to the development of new diagnostic and therapeutic strategies. Dr. Tuveson focuses on pancreatic ductal adenocarcinoma (PDAC), the most lethal common cancer with a 5-year survival rate of only 6%. His lab developed the first mouse models of PDAC, which have been instrumental in the discovery of biomarkers of early disease; identified pathways and druggable targets involved in the initiation, progression and metastasis of PDAC; and developed new therapeutic strategies. Following his observation that PDAC tumors contain a deficient and compressed vasculature, which limits drug delivery and therefore efficacy, Dr. Tuveson has uncovered several methods to correct or target these vascular deficits and promote drug response. This has led to the initiation of several clinical trials. At CSHL, he continues the search for new vulnerabilities in PDAC neoplastic cells and the tumor surroundings, called the microenvironment. His team will evaluate candidate drug targets in an advanced testing facility being developed as part of the CTI.

Jesse Gillis

Jesse Gillis, Ph.D.

Assistant Professor

The Gillis laboratory is working to understand how genes interact, relating to gene function and the effect on disease. Using computational biology and data derived from gene association studies, he interprets the functions of genes in the context of the networks they form. Historically, attempts to understand gene function through networks make use of a principle known as "guilt by association" (GBA). This concept implies that genes with related functions tend to share properties (e.g., physical interactions). GBA has become a favored way to grapple with the complex genetic interdependencies in the face of floods of genomics and proteomics data. Dr. Gillis is making fundamental improvements to GBA, applying it to neuropsychiatric gene network data to understand disease.

Molly C. Hammell, Ph.D.

Assistant Professor

The Hammell laboratory is interested in understanding — on a system-wide basis — how multiple types of regulatory factors in cells interact within and among gene networks. Dr. Hammell uses computational algorithms to integrate multiple types of profiling data gathered from genomes and "transcriptomes" — readouts of all genes active in a given cell at a particular moment in time — to develop models of regulatory circuits in human disease. Her team is creating new tools for the statistical analysis of high-throughput data, novel algorithms for modeling the flow of signals through genetic pathways, and testing these models using the tools of molecular genetics. The goal is to understand how human diseases like cancer take advantage of the cell's innate adaptability by rewiring its regulatory networks.

Christopher R. Vakoc

Molly C. Hammell

Ivan Iossifov, Ph.D.

Assistant Professor

The Iossifov laboratory studies the genetics of common diseases in humans using two main tools: next-generation sequencing and molecular network models, which represent functional relationships among specific locations along the genome, called genetic loci. The laboratory applies advanced machine learning and statistical modeling techniques to analyze massive amounts of biomedical data. Used in combination, these tools enable Dr. Iossifov and colleagues to conduct the large-scale studies necessary for furthering our understanding of complex diseases such as autism, bipolar disorder and cancer.

Gholson J. Lyon, M.D., Ph.D.

Assistant Professor

The Lyon laboratory focuses on analyzing human genetic variation and its role in severe neuropsychiatric disorders by studying large groups of related individuals living in the same geographic location. Dr. Lyon's lab is utilizing sequencing of whole genomes and of the exome — the small portion of the genome that encodes proteins — to find mutations that distinguish disease syndromes in populations from Utah and elsewhere. He is interested in the discovery of families with rare diseases and/or increased prevalence for syndromes such as Tourette syndrome, ADHD, obsessive compulsive disorder, mental retardation, autism and schizophrenia.

Christopher R. Vakoc, M.D., Ph.D.

Assistant Professor

The Vakoc laboratory investigates how molecules that regulate chromatin are integrated within the cancer-promoting signaling pathways that drive cancer cell growth. Chromatin is the combined package of DNA and proteins around which it is coiled within the nucleus of cells. The lab's focus is on acute myeloid and lymphoid leukemias, and is expanding its research on epithelial tumors. Dr. Vakoc employs genetically engineered mouse models of cancer that recapitulate the main features of human disease, particularly with respect to therapeutic response. Through a genetic screen, the laboratory recently identified a protein called Brd4 as a critical vulnerability in acute myeloid leukemia — a protein the cancer depends upon for its survival. Brd4 helps control the pattern of which genes are switched on and how they work. Dr. Vakoc's work coincided with the independent development of small-molecule drug inhibitors of Brd4 and related proteins. Using these agents, he has pharmacologically validated Brd4-inhibition as a therapeutic strategy in preclinical animal models of leukemia and his findings are being tested in clinical trials.

Passing the WSBS torch

Leemor Joshua-Tor, Ph.D., the outgoing Dean of the Watson School of Biological Sciences (WSBS), completed her five-year term this year. As the third leader of a school known as one of the nation's most innovative Ph.D.-granting programs, Dr. Joshua-Tor has advanced the curriculum in significant ways, including the addition of timely courses in quantitative biology, physical biology, and imaging. She has also served during her term as a member of the Biomedical Workforce Task Force of the U.S. National Institutes of Health, which recently issued recommendations to support a future sustainable biomedical research infrastructure. Dr. Joshua-Tor, a structural biologist who began her career at CSHL in 1995, is an Investigator of the Howard Hughes Medical Institute. She has made seminal contributions to the understanding of how RNA interference works to silence gene expression and has advanced new therapeutic options for combatting papillomavirus, which causes cervical cancer. Dr. Joshua-Tor will continue her research at the Laboratory, studying the molecular basis of cell regulatory processes using the tools of structural biology and biochemistry.

CSHL Professor Alexander A.F. Gann, Ph.D., is the fourth Lita Annenberg Hazen Dean of the WSBS, effective January 2013. Dr. Gann has served as Editorial Director of the Cold Spring Harbor Laboratory Press, where since 1999 he has produced publications ranging from textbooks for undergraduate and graduate education to laboratory manuals and books on the history of science. He is a co-author of *Molecular Biology of the Gene*, now in its 6th edition, and of the recently released *Annotated Double Helix*, a new edition of James D. Watson's autobiographical classic. Dr. Gann received his Ph.D. from the University of Edinburgh in 1989, after which he continued his postdoctoral training at Harvard and University College, London, and lectured at Lancaster University. A longtime member of the WSBS faculty, Dr. Gann brings a unique combination of inside perspective and broad understanding of the impact of the digital and genomic revolutions upon higher education and the biological sciences.

Dagnia Zeidlickis

Celebrating science

Members of the Board of Trustees
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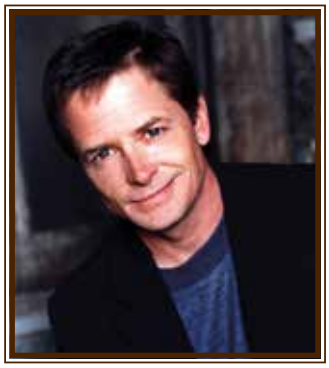

Michael J. Fox
activist for Parkinson's
disease research

Arthur D. Levinson
pioneer in biotechnology
development

Mary D. Lindsay
leader in health and science
philanthropy

gala hosted by Deborah Norville
with a performance by Joshua Bell and Frederic Chiu

the november 28, 2012 event at the mandarin oriental new york raised
$3.5 million for cshl research. thanks to event chairmen:

Mr. and Mrs. Lee S. Ainslie III
Ms. Jamie C. Nicholls and Mr. O. Francis Biondi, Jr.
Dr. Herbert W. Boyer
Mr. and Mrs. Robert D. Lindsay
Mr. and Mrs. Marc S. Lipschultz
Dr. Richard H. Scheller
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Mr. and Mrs. Remy W. Trafelet

for videos and images visit **www.doublehelixmedals.cshl.edu**

Faculty & Friends

President's Council on ethical dilemmas in medicine

Members of the CSHL President's Council who donate in support of the exceptionally talented and motivated young scientists known as CSHL Fellows gathered at the Banbury Conference Center facility on October 12–13 to explore topics in medical ethics. Experts addressed issues ranging from overdiagnosis by physicians and cancer profiling to research with incapacitated human subjects and the American eugenics movement. CSHL Director of Research David L. Spector and Associate Professor Lloyd Trotman headed the agenda, which also included DNA Learning Center Executive Director David Micklos. CSHL Trustee Andrew Solomon, acclaimed writer on politics, culture and society, discussed his new book, *Far from the Tree*, about raising children with exceptional physical, psychological, emotional and social challenges. Guest speakers included Drs. Gilbert Welch of Dartmouth, Jeffrey Berger of Stony Brook University and Hans Sauer of the Biotech Industry Organization. CSHL Trustee Howard L. Morgan and Cynthia R. Stebbins co-chaired this year's council retreat.

DuPont Pioneer, CSHL renew plant collaboration

CSHL and DuPont Pioneer have renewed another five-year multi-million-dollar collaboration to conduct plant biology research focused on meeting growing food demands worldwide. The agreement seeks to more fully understand the genetic basis of fundamental plant processes controlling growth, development and yield. According to Rob Martienssen, CSHL professor and Howard Hughes Medical Institute Investigator, "as scientists, we get excited about seeing our discoveries translated into real-world applications. It is clear that basic research in these areas has the potential to radically change the face of the agricultural industry." From the industry perspective, John Bedbrook, Vice President of DuPont Agricultural Biotechnology, contends that "the collaboration has increased our understanding of the basic genetic mechanisms controlling plant growth and development, which will contribute to global food security in the coming decades."

Pfizer and CSHL join forces to identify cancer targets

CSHL has announced a research collaboration with Pfizer Inc. to develop a next-generation human short-hairpin RNA (shRNA) library that will silence gene expression via the process of RNA interference (RNAi) and help identify new therapeutic targets in cancer. The agreement will bring the Laboratory's researchers together with Pfizer's scientists in both the technology development and training environments. "Pfizer is pleased to be involved in this partnership, which will marry cutting-edge shRNA technologies with our efforts in cancer genetics and complex tumor models toward the singular goal of identifying and validating novel targets for cancer therapeutics," said Bob Abraham, Pfizer's Oncology Chief Scientific Officer. CSHL is the birthplace of the first-generation shRNA library developed by HHMI Investigator and CSHL Professor Greg Hannon, who pioneered the use of RNAi techniques to study mammalian genes and developed synthetic shRNAs to silence the expression of most human, mouse, and rat genes.

11th annual Women's Partnership luncheon

CSHL Professor Michael Wigler informed and entertained an audience of 180 at the 11th annual Women's Partnership luncheon, predicting that "in a few years' time, we will be able to walk in to a doctor's office, they will draw a blood sample, and there will be a fairly routine and inexpensive test that will tell you if you have cancer, and if so, in which part of your body." The event, which over the years has raised $800,000, unites prominent women from New York society in celebration of women pursuing biomedical research careers at CSHL. 2012 co-chairs were Elizabeth Ainslie, Gabrielle Bacon, Meg Braff, Lisa Eastman, Simone Mailman, Cristina Mariani-May, Louise Parent, Hope Smith and Mary Snow. "We are grateful to the Women's Partnership for having created a first-rate opportunity for scientists and citizens to come together," said President Bruce Stillman. Special thanks to former CSHL trustee and honorary chair of the event Kristina Perkin Davison.

Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

Economic impact

Gov. Cuomo calls CSHL 'a place of inspiration'

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New York Governor Andrew Cuomo and Lt. Governor Robert Duffy visited CSHL October 5 as part of a statewide tour of economic development success stories. CSHL Professor David Tuveson briefed the dignitaries on the Laboratory's Cancer Therapeutics Initiative, which New York State is helping to fund by seeding the construction of a new Advanced Drug Testing Facility at CSHL's Woodbury Genome Center. Key to the initiative is translation of advanced basic research such as that performed in the Tuveson lab to the development and validation of novel cancer drug targets and candidate compounds. Praising CSHL's cancer research program, Cuomo went on to say, "What it does for the soul, the people it gives hope to — because Cold Spring Harbor has always been synonymous with accomplishing the impossible — It really is an inspiration for me personally to be here."

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