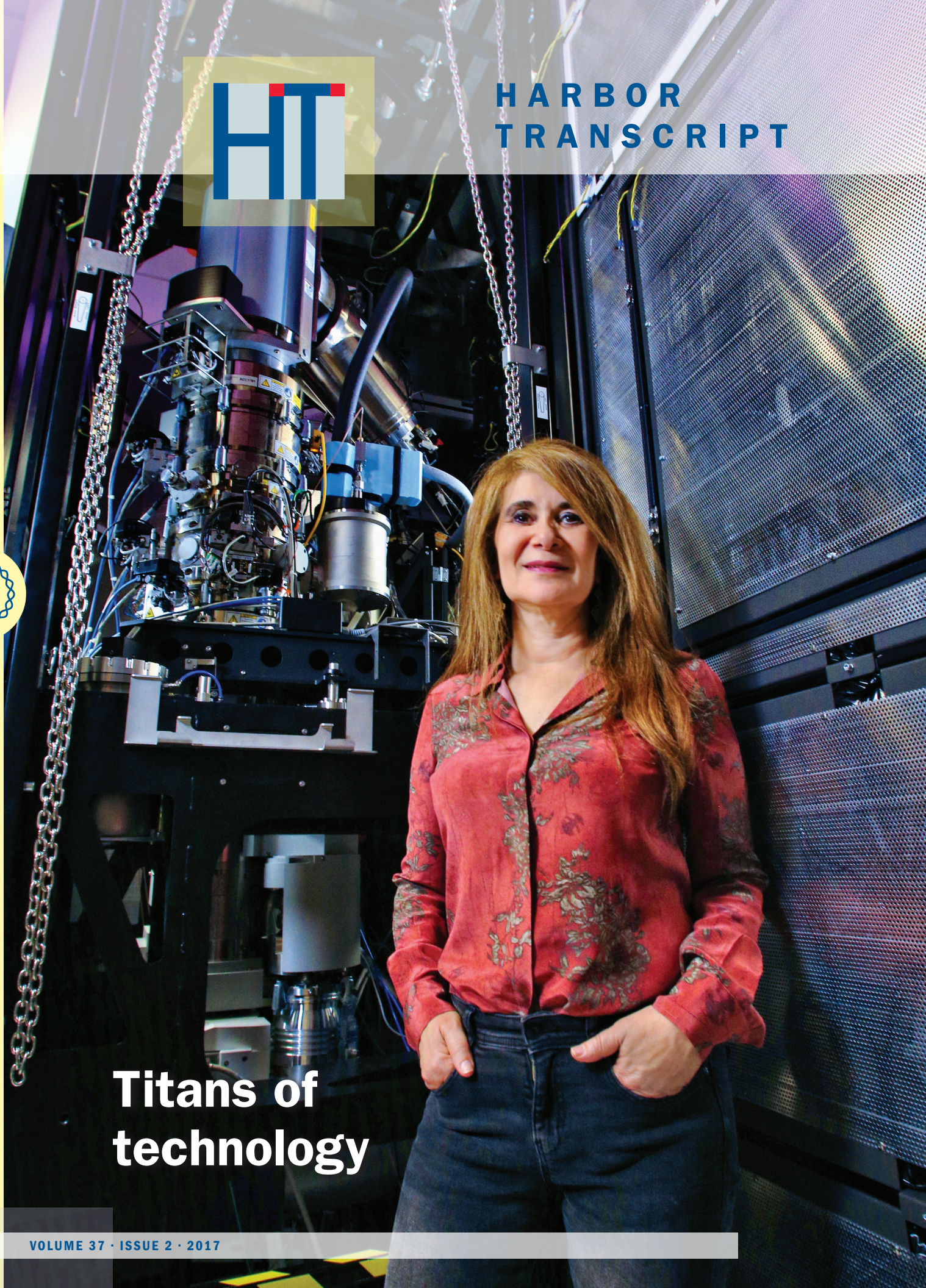


HARBOR TRANSCRIPT

Cold Spring Harbor Laboratory

Titans of technology

VOLUME 37 · ISSUE 2 · 2017

Cold Spring Harbor Laboratory

HARBOR TRANSCRIPT

Volume 37 · Issue 2 · 2017

PRESIDENT'S MESSAGE

During a recent visit, New York Governor Andrew Cuomo called Cold Spring Harbor Laboratory "hallowed ground" for science. State Senator Carl Marcellino, hailing CSHL as a "jewel of Long Island," made a very important point: it's not the buildings or the campus that make CSHL great, it's the people who work, study, and train here that define the Laboratory's value. I couldn't agree more.

So as you read this magazine, focus on the people. These pages are about some of CSHL's many leaders—titans who innovate and advance the frontiers of biology in their own areas of expertise. Professor Leemor Joshua-Tor is a powerful example of a faculty member who has made invaluable contributions to the Laboratory's prowess in both research and education. A Howard Hughes Medical Institute Investigator, she has made seminal discoveries in structural biology and simultaneously has been instrumental in the design of Ph.D. programs at CSHL and across the country.

Professor Mike Wigler and Associate Professor Alex Krasnitz are pioneers of single-cell sequencing and have harnessed this technology to probe cancer, one cell at a time. Now they have devised a method to detect nascent tumors at the earliest opportunity—when they are most likely curable. It all starts with a simple draw of blood that you might provide at an annual physical.

Kudos to our neuroscientists whose innovative approaches to understanding the brain have won them national and international acclaim. See "One Experiment" for a beautiful image of a brain from Associate Professor Pavel Osten. It represents just one of the accomplishments of many CSHL neuroscience investigators who led the field this year in securing numerous and significant National Institutes of Health BRAIN Initiative grants.

These are just a few examples of contributions from the people who make up Cold Spring Harbor Laboratory, reminding us of why we are a world-leading research and education institute. Add to our campus population the more than 9,000 annual visiting scientists who define CSHL as the mecca for the exchange of information in life science. Please keep informed using our new website, which provides easy access to the latest stories and news about the many faces of CSHL.

Bruce Stillman

Harbor Transcript

Volume 37, Issue 2, 2017

Harbor Transcript is published by the Department of Public Affairs of Cold Spring Harbor Laboratory.

Public Affairs
One Bungtown Road
Cold Spring Harbor, NY 11724

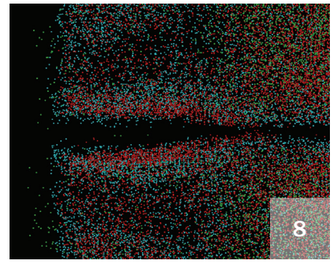
516.367.8455
publicaffairs@cshl.edu

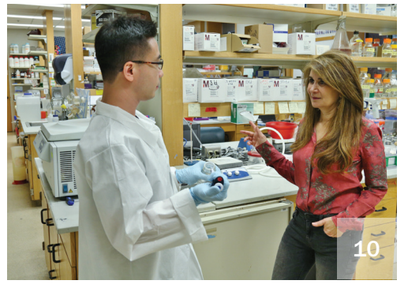
www.cshl.edu

V.P. Communications:
Dagnia Zeidlickis
Managing Editor:
Phil Renna
Writers:
Andrea Alfano
Brian Stallard
Peter Tarr
Design & Layout:
Margot Bennett
Photography:
©Bob Giglione/CSHL: front cover, 1–2, 12, 16;
©Charles Camarda: inside front cover;
©Bigstock/Yakobchuk Olena: 3;
©Kayla Erb/CSHL: 6;
Courtesy CSHL Archives: 7, 12;
Courtesy Osten lab: 1, 8–9;
©Constance Brukin/CSHL: 10, 13–16;
Courtesy Joshua-Tor lab: 11;
Courtesy Brookhaven National Laboratory: 13;
©Thomas Adams, 2017/CSHL: 14;
Virginia Sherwood/NBC: inside back cover;
Courtesy Lustgarten Foundation: inside back cover

Illustration:
Courtesy Krasnitz lab: 4–5;
Courtesy Joshua-Tor lab: 10;
Courtesy Chan-Zuckerberg Initiative: 15;
©Margot Bennett & Gina Motisi/CSHL: back cover

Visit www.cshl.edu to sign up for our monthly email newsletter.





FEATURES

FACULTY & FRIENDS

On the cover and on the web:
"As biology becomes more molecular, it is becoming more defined," says CSHL Professor Leemor Joshua-Tor. She has mastered technologies that allow her to use the shape of molecules to figure out what they do and how they work. Joshua-Tor is pictured alongside a cryo-electron microscope, with which she can see atomic-level 3-dimensional images. This is just one example of powerful technology scientists harness to advance biology.

A transformative partnership

"We're at Cold Spring Harbor Laboratory today, which is hallowed ground for scientific research. You can almost *feel* when you walk on the grounds that you're in a special place and great things have happened here," said New York State Governor Andrew Cuomo on October 12. "The potential we have on Long Island in this biomedical field and biotechnology field is, I think, unprecedented."

Flanked by a who's who list of Long Island elected officials and economic development colleagues, the Governor headlined the ground-breaking for the renovation of the historic Demerec Laboratory. To be completed by the end of 2018, the facility will be the nucleus of a $75 million CSHL initiative to advance therapeutic development for breast cancer, leukemia, autism, obesity/diabetes and lung cancer. New York State is providing a $25 million grant toward infrastructure for the initiative called the Center for Therapeutics Research (CTR).

"New York is a leader in next-generation technology and sciences, and with the ground-breaking of the new Center for Therapeutics Research in Cold Spring Harbor, we are supporting developments in research and medicine that will save lives," Cuomo said. "The Center will create new jobs, broaden our understanding of medicine and treatment, and secure Long Island's place as a hub for life science research that will support a stronger, healthier New York for all," said Cuomo.

"With the help of Governor Cuomo, Senator Marcellino, and our public and private sectors, Cold Spring Harbor Laboratory (CSHL) will continue to transform the way basic science research is done, searching for answers to science's most important challenges and that will positively change the lives of children and adults suffering from disease," said CSHL President & CEO Bruce Stillman.

New York State Senator Carl L. Marcellino said, "The work that we are here to foster, to improve and increase is monumental. The future is before us and it's bright because of what the men and women researchers of this fantastic facility are doing. This place provides hope. It's not the buildings, it's not the cement, or the steel or the bricks and mortar we're talking about here, it's the people, the researchers who work in those laboratories, who do the work, who make the discoveries...it is one of the jewels of Long Island."

Dagnia Zeidlickis

Next-gen cancer test

Knowing that cancers become lethal when they spread, investigators at Cold Spring Harbor Laboratory (CSHL) seek a way of detecting tumors much earlier than now possible—when they're more likely to be curable. Fleshing out an idea Professor Michael Wigler had years ago—before there was technology to act on it—research led by Associate Professor Alexander Krasnitz has advanced an inexpensive method to do just this. It begins with a simple blood draw like that performed at an annual physical.

X-rays, MRI and CT scans, as well as biopsies, have helped detect certain cancers earlier. The next-generation technology is a blood test—*sensitive* enough to consistently find the earliest, invisible cancers, and *accurate* enough to avoid false positives and negatives.

Publishing in *Trends in Molecular Medicine* this year, Krasnitz, Wigler and colleagues proposed such a blood screen. They tested it "in silico," *i.e.*, by plugging real data into a mathematical model they devised. The data came from 3,852 patients with 11 types of solid tumors, whose cases are archived in The Cancer Genome Atlas (TCGA). The results were encouraging, suggesting that the CSHL early detection method is feasible—both accurate and sensitive enough to find many kinds of solid cancers, perhaps when they are still invisible, and at around $1,000 per test—a number certain to come down with the cost of DNA sequencing.

There is a critical supposition in the team's demonstration. Buoyed by a growing body of evidence that even very early tumors shed cells into the blood, they assume that 10 related tumor cells will be present in a typical 50 billion-cell 10 ml blood draw (about 2 teaspoons' worth). The team assessed their proposed method by assuming it was able to find 6 of the 10 expected tumor cells in a known cancer patient's blood sample.

The computerized test of the CSHL early detection method showed that it detects most common solid tumor types with great sensitivity. Krasnitz and colleagues calculated they would have detected nearly 100% of the 457 ovarian cancers and 261 small-cell lung cancers in the TCGA sample; roughly 90% of the 750 breast cancers, and 70%–75% of the 485 glioblastomas and 349 colon tumors. Tumors that tend to have fewer copy number variations, or CNVs—one of the two cancer hallmarks the method is based on—were harder to detect: about 55% of 373 kidney tumors and 378 uterine tumors. But the method's ability to accurately detect very early ovarian and lung cancers is particularly good news, since both are notorious for being diagnosed at an advanced stage.

The CSHL method is distinguished from other "liquid biopsy" tests now in development, which sift for fragments of mutated DNA floating in the blood. The weakness of that approach, says the CSHL team, is precisely its dependence upon fragmentary evidence—"cell-free" DNA that has detached from the cells it came from. "It usually takes multiple genetic hits to initiate cancer," Krasnitz explains, "and one problem with looking at cell-free DNA is that you don't know, assuming you find two or more suspicious fragments, whether they came from the same cell or not. If they don't, the 'signal' could be spurious."

To be useful, Krasnitz stresses, clinicians need to be able to follow up on positive results in a meaningful way. Because it is based on the capture and analysis of intact cells, the CSHL method can readily trace suspect cells to their tissue of origin, by reading their epigenetic profile (chemical marks on the DNA that vary by cell type) or by sequencing RNAs generated by active genes (similarly varying according to cell and tissue type). These tests add cost, but would only be performed in the minority of cases in which there is evidence of clonality—a second cancer hallmark necessary for a positive result in the CSHL method.

If closer analysis points to the lung, or to the breast, for example, still more expensive high-resolution scans and biopsies can be used to spot early tumors, which might then be treated and possibly cured. Unlike most biopsies now performed, those occasioned by the new screening method would likely be ordered before a single symptom appeared—as the result of a routine screen performed at an annual check-up.

This is precisely the grail that the medical community has long sought—to find and treat cancers before they become lethal. The next step, says Krasnitz, is to test the accuracy of the method in a clinical study involving patients just diagnosed with cancer. The use of a blood screen as a cancer preventive given at a yearly physical is still a few years down the road. It would first be used in patients who have already been treated for cancer, to detect recurrence, or as a preventive in people known to be at high risk for particular cancer types, such as HER-2-positive breast cancer.

Peter Tarr

How it works

The CSHL early detection method features a technology called **single-cell sequencing**, which generates a genome-wide copy number profile of each cell. These profiles register copy number variations, or CNVs: places in the genome where there is extra or missing DNA. Everyone has CNVs in their genome, but they're almost always harmless. In cancer cells, the genome is highly disturbed and CNVs abound. **An irregular copy number profile** is one of the hallmarks of cancer that the CSHL early detection method looks for.

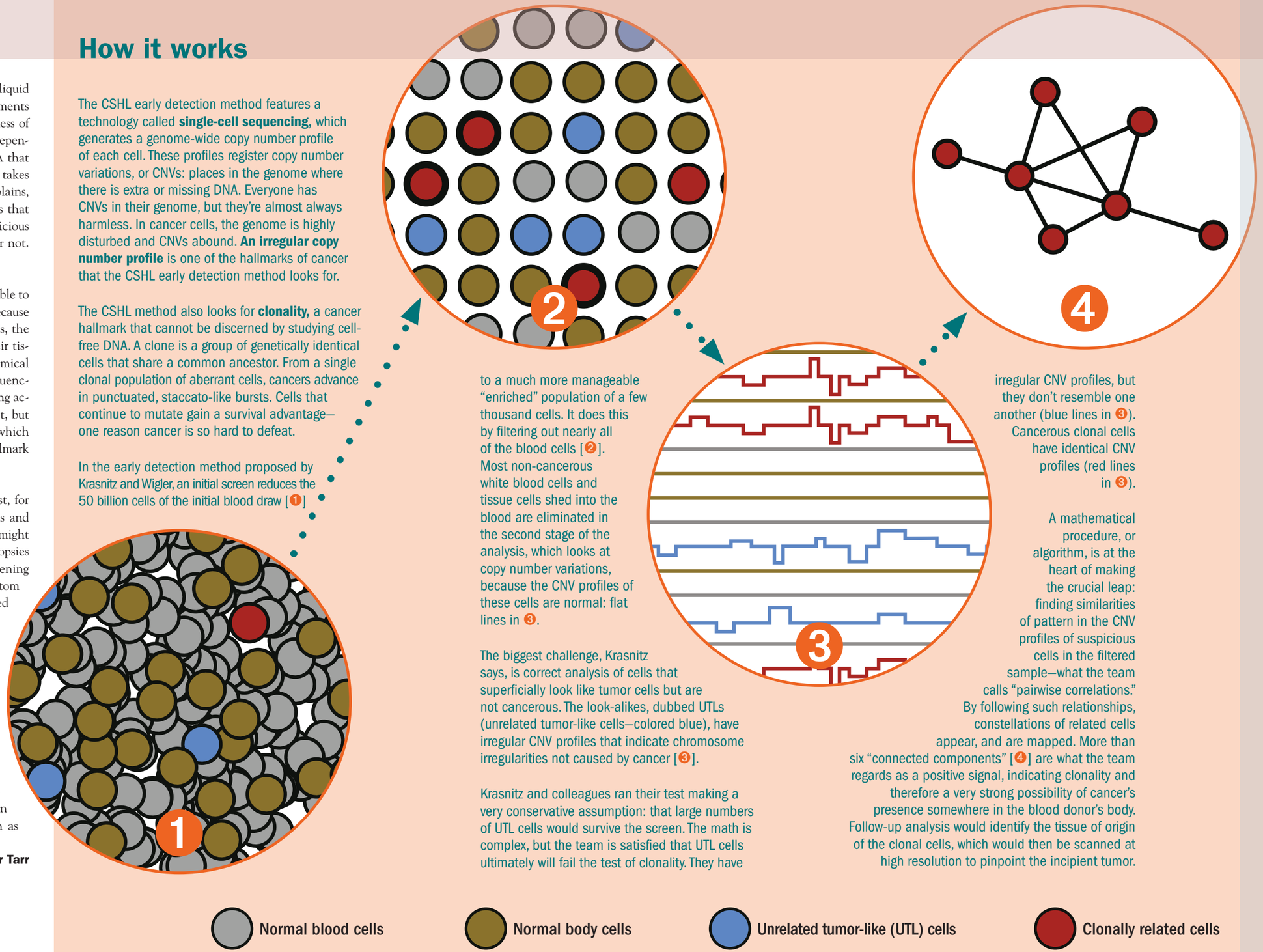
The CSHL method also looks for **clonality,** a cancer hallmark that cannot be discerned by studying cell-free DNA. A clone is a group of genetically identical cells that share a common ancestor. From a single clonal population of aberrant cells, cancers advance in punctuated, staccato-like bursts. Cells that continue to mutate gain a survival advantage—one reason cancer is so hard to defeat.

In the early detection method proposed by Krasnitz and Wigler, an initial screen reduces the 50 billion cells of the initial blood draw [1] to a much more manageable "enriched" population of a few thousand cells. It does this by filtering out nearly all of the blood cells [2]. Most non-cancerous white blood cells and tissue cells shed into the blood are eliminated in the second stage of the analysis, which looks at copy number variations, because the CNV profiles of these cells are normal: flat lines in 3.

The biggest challenge, Krasnitz says, is correct analysis of cells that superficially look like tumor cells but are not cancerous. The look-alikes, dubbed UTLs (unrelated tumor-like cells—colored blue), have irregular CNV profiles that indicate chromosome irregularities not caused by cancer [3].

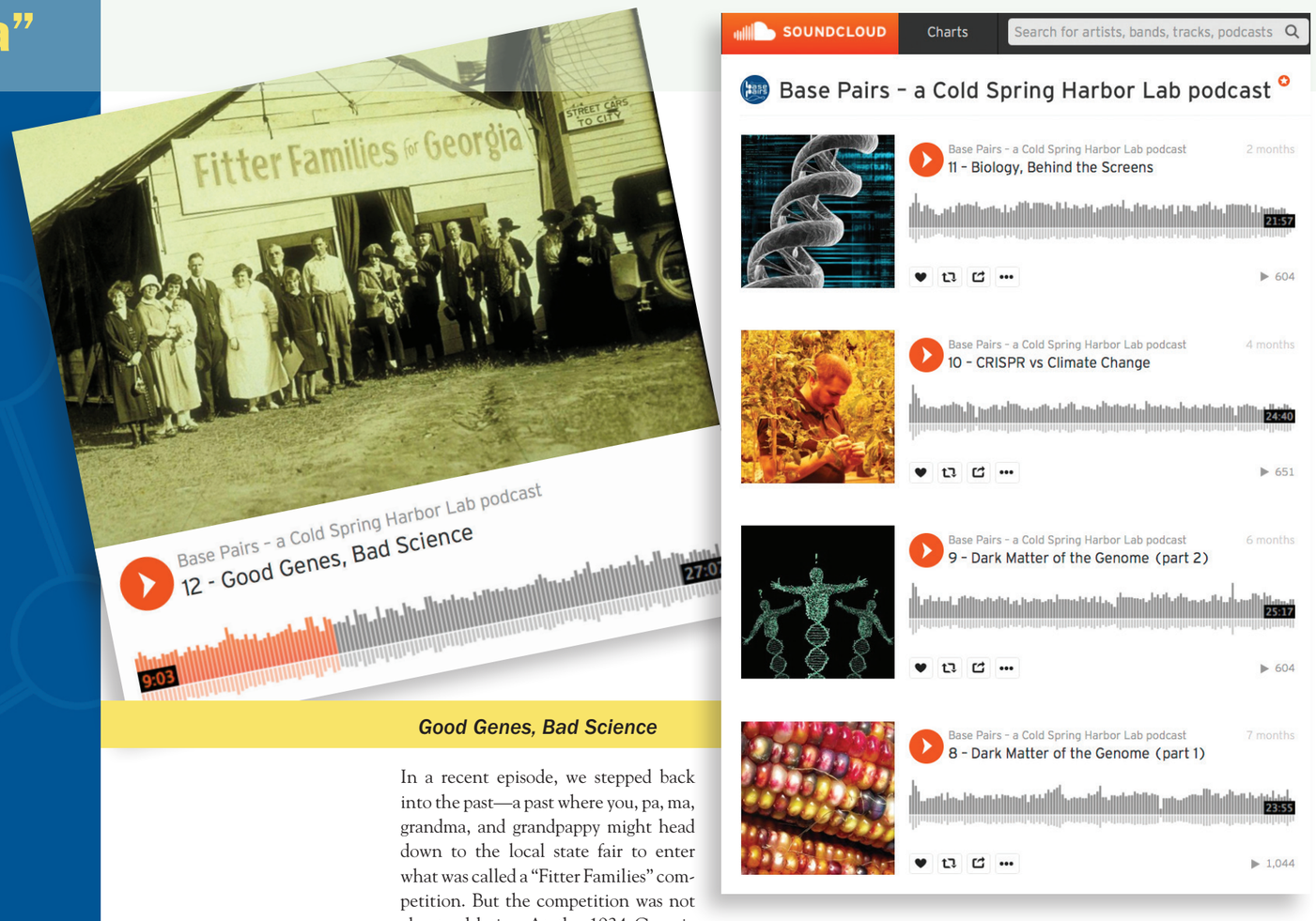
Krasnitz and colleagues ran their test making a very conservative assumption: that large numbers of UTL cells would survive the screen. The math is complex, but the team is satisfied that UTL cells ultimately will fail the test of clonality. They have irregular CNV profiles, but they don't resemble one another (blue lines in 3). Cancerous clonal cells have identical CNV profiles (red lines in 3).

A mathematical procedure, or algorithm, is at the heart of making the crucial leap: finding similarities of pattern in the CNV profiles of suspicious cells in the filtered sample—what the team calls "pairwise correlations." By following such relationships, constellations of related cells appear, and are mapped. More than six "connected components" [4] are what the team regards as a positive signal, indicating clonality and therefore a very strong possibility of cancer's presence somewhere in the blood donor's body. Follow-up analysis would identify the tissue of origin of the clonal cells, which would then be scanned at high resolution to pinpoint the incipient tumor.



“Hi, my name is Brian”…“and I’m Andrea”

We’re the hosts of *Base Pairs*, a podcast from Cold Spring Harbor Laboratory that tells stories about the power of genetic information—past, present and future. With two seasons of episodes available on demand, it’s clear that our idea to focus on genetic information opens endless possibilities for discussion. It’s part of our daily lives, from the food we put on our tables to our ancestry and how we are related to the very earliest humans, our mental and physical health and healthcare decisions, the ability of living things to adapt to a changing global environment, and even social policy and the justice system. The list goes on…



Good Genes, Bad Science

In a recent episode, we stepped back into the past—a past where you, pa, ma, grandma, and grandpappy might head down to the local state fair to enter what was called a “Fitter Families” competition. But the competition was not about athletics. At the 1924 Georgia State Fair, for example, families happily lined up to be judged on their breeding, just like livestock!

Competitions like this one were held in the name of eugenics, a belief system based in pseudoscience aimed at improving the human gene pool. Built on observations of spurious traits like “feeble-mindedness,” the eugenics movement associated social inadequacies with genetics, resulting in policies to limit reproduction by people judged inadequate.

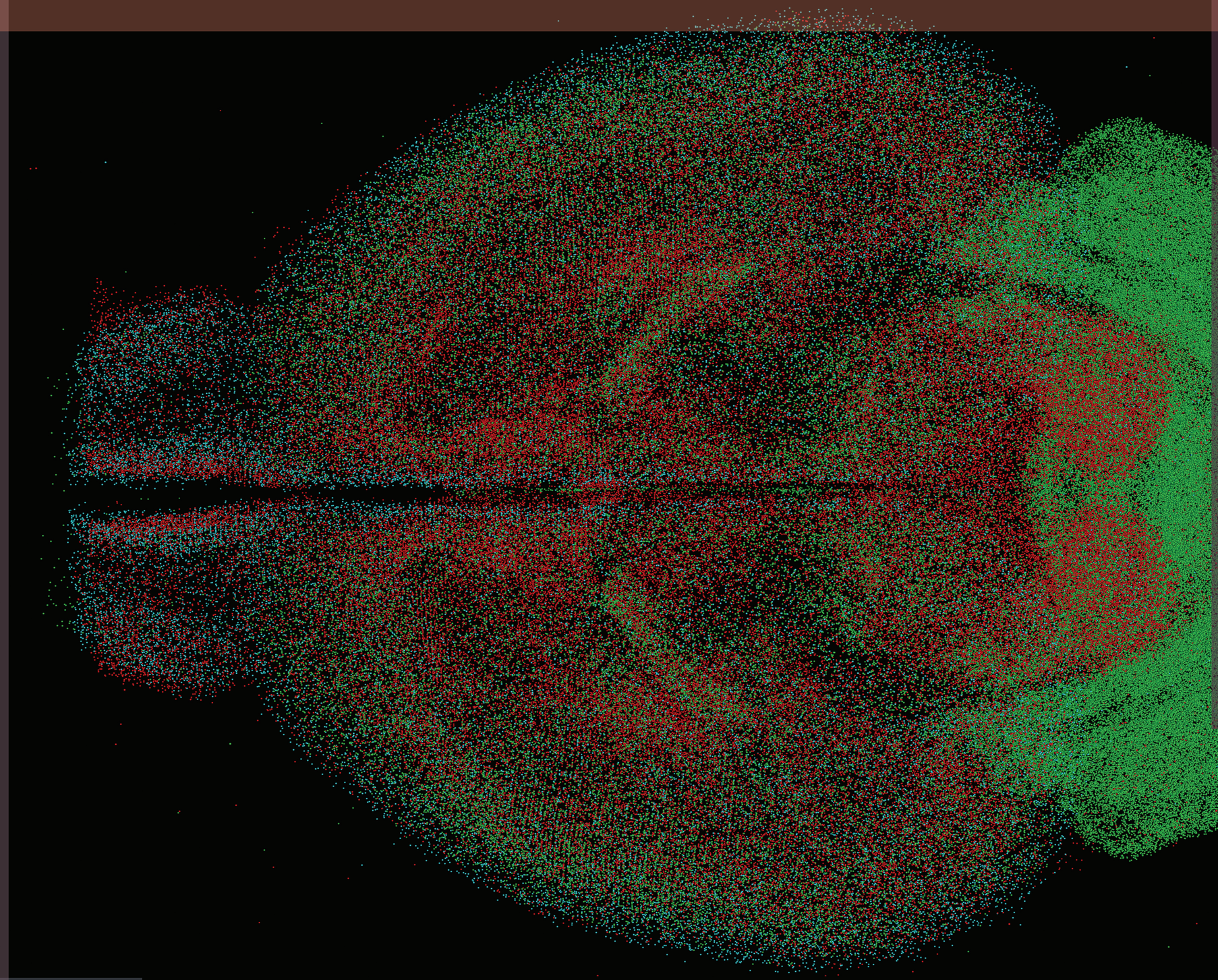
Today, there’s some huge new science that’s making this unsettling American history an urgent issue again. With new gene editing tools like CRISPR beginning to be used to change the *human* genome, do we risk repeating history?

To probe how to avoid the unscientific traps that gave rise to the American eugenics movement, the episode “Good Genes, Bad Science” interviews Jennifer Doudna, co-creator of the revolutionary CRISPR gene editing tool; David Micklos, executive director of CSHL’s DNA Learning Center and creator of the online Eugenics Archive; and Miriam Rich, a doctoral student studying the history of science and medicine, supported by CSHL Archive’s Sydney Brenner Research Scholarship.

The best part is, you can get up to speed on what is arguably the most important ethical conversation in biology even while driving to work or cleaning the house. That’s because podcasts are an on-demand form of radio. You can search for *Base Pairs* on Apple Podcasts, Stitcher, SoundCloud, or Google Play Music from your smart phone. You can also listen and explore a treasure trove of multimedia extras at: labdish.cshl.edu/GoodGenes

Put the “smart” back in smart phone and check out the show!

One experiment



What you see here is not a pointillist masterpiece. It is a rendering of the mouse brain, from above, formed by millions of colored dots. Like the famous canvases painted by post-Impressionist Georges Seurat, the triumph of this image is in the relation of the dots themselves. Each colored dot is an inhibitory neuron, and what Associate Professor Pavel Osten and colleagues discovered using their qBrain method is discerned by probing hidden relations among the dots—a task not for the eye but for quantitative biologists and supercomputers.

The "q" in qBrain stands for quantitative. This first-ever map of the whole mouse brain at single-cell resolution enables scientists to make accurate counts of specific nerve-cell types. "The brain is like a very complicated Lego puzzle," Osten says, "with pieces that come in all sorts of shapes and sizes. If you want to understand how brain circuits work, you first need to know how many pieces there are, of what types, and how they're distributed." Mapped here are three types of inhibitory cells, expressing proteins called PV (green), SST (red) and VIP (blue).

This proof of principle bodes well for CSHL's leadership role in the NIH's multi-year BRAIN Initiative, in which Osten and Professor Josh Huang are principal investigators and four other faculty (Zador, Mitra, Albeanu and Gillis) are core leaders and/or co-investigators. In one experiment made possible by qBrain, Osten's team disproved a widely held assumption that inhibitory neuron types are evenly distributed across the cortex. Another experiment showed that male brains, despite their larger average size, don't contain more inhibitory cells than female brains. In 10 subcortical regions, females have more, meaning they have finer control over areas regulating reproductive, social and parenting behaviors. These are surely the first of many important discoveries.

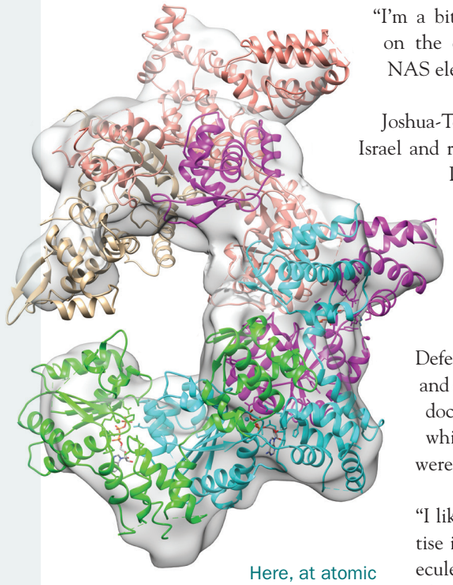
Peter Tarr

RESEARCH PROFILE

Leemor Joshua-Tor

When she was in the 7th grade, Leemor Joshua-Tor came upon a fragrant box that once held her mother's perfume. It proved the perfect container for a set of flash cards that she was using to learn properties of the chemical elements. "I think my brain connected doing chemistry to good feelings, good smells," she muses of the fortuitous association.

A CSHL faculty member since 1995, a professor since 2005, an Investigator of the Howard Hughes Medical Institute (HHMI) since 2008, as well as Dean of the Watson School of Biological Sciences for a 5-year period, Joshua-Tor is among the most distinguished members of the Laboratory community. In 2017, the structural biologist received the high honor of being elected to the National Academy of Sciences (NAS) *and* to the American Academy of Arts and Sciences. "I'm a bit overwhelmed," she admitted on the day she was informed of her NAS election.



Here, at atomic resolution, the multi-part protein complex, ORC, that performs the first step in genome replication.

Joshua-Tor was born in Rehovot, Israel and returned there to study for her Ph.D. at the world-famous Weizmann Institute of Science. She had already distinguished herself at Tel-Aviv University and in three subsequent years as an officer in the Israeli Defense Forces, involved in research and development. She did her postdoctoral research at Caltech, by which time her interests in science were pretty clear.

"I like to tell people that my expertise is looking at the shape of molecules and understanding from that what they do and how they work," she says. Not just any molecules, but ones of fundamental importance that lie at the heart of life processes.

"I like molecules—they have always seemed…definitive to me," she says. Biology at first seemed a bit "squishier" than chemistry, a comparison that helps explain her interest in relating biological structure and function. "I think that as biology becomes more molecular, it is becoming more defined," she says, approvingly—implying that as it does, life itself is becoming better understood.

Titan of technology

While in graduate school, Joshua-Tor drew upon strengths in computation and chemistry. She was soon working on tools to study nucleic acids, the biomolecules that are the building blocks of life. In subsequent years she applied her skills in chemistry to mastering x-ray crystallography, the method that famously had been used to solve the structure of DNA and many important proteins. It involves shooting a high-energy beam of x-rays through molecules as a means of revealing their shape, down to the level of individual atoms. Today, Joshua-Tor is using a cryo-electron microscope, where an electron beam is passed through a rapidly frozen specimen—no crystal necessary—to obtain a near atomic-level 3-dimensional image. The key developers of the method, which is now widely used, received the 2017 Nobel Prize for Chemistry.

Around the time Joshua-Tor arrived at Cold Spring Harbor Laboratory in the mid-'90s, the biology community was just learning about a fundamental cellular process called RNA interference (RNAi). Through RNAi, cells in a wide variety of organisms—yeasts, plants, animals—are able to regulate the output of their genes. By the early 2000s, Joshua-Tor and colleagues including Rob Martienssen and Greg Hannon were using biochemical and structural methods to lay bare the mechanism that enabled RNAi to silence genes in a highly specific manner.

In 2003 they provided a first-ever glimpse into the molecular structure of a piece of the RNAi machinery, one domain of a large protein (now understood to be an enzyme) that interacts with messenger RNAs. mRNAs are messages from genes, bearing instructions for building specific proteins. Joshua-Tor was working toward crystallizing and solving the complete structure of that protein, an RNAi component called Argonaute.

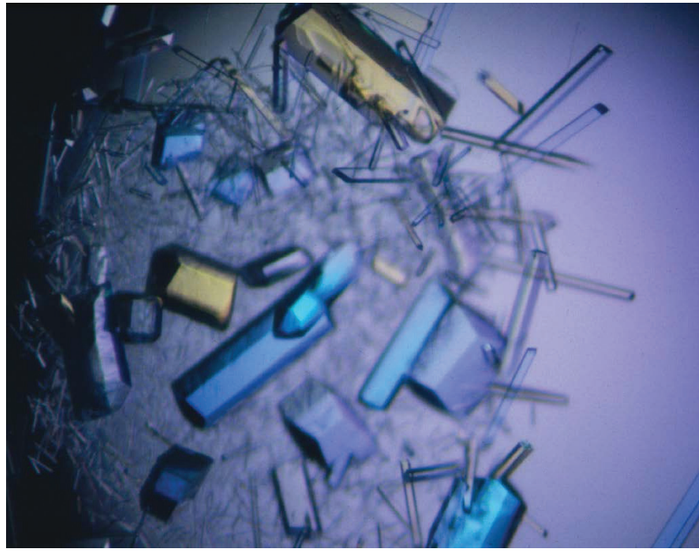
There were theories about how RNAi actually works to tamp down gene expression. Her team's full Argonaute structure, published in 2005, definitively solved a key part of the mystery: the protein features a groove into which tiny guide sequences of RNA can nestle. Armed with an RNA guide strand, Argonaute can be programmed by the cell to seek out specific mRNAs, bind them, and then via enzymatic action, slice them up. Interfering in this way with the process in which DNA is transcribed into an RNA protein blueprint, Argonaute proves to be the catalytic element—the "slicer" that prevents a protein from being made.

Joshua-Tor's lab continues to work on Argonaute, which has eight structural variants in the human system alone and whose ability to fine-tune the output of our genes can mean the difference between health and sickness, even life and death. Another of the lab's achievements is its success in explaining how a six-sided protein ring called helicase—essential in all life—attaches to the double helix and works like a tiny motor, unzipping the two DNA strands as other molecular machines go about copying one of them. It's a central part of the process in which one cell becomes two.

"We have shown how the separation in the two strands gets propagated," explains Joshua-Tor, "but we still don't really understand how the double helix is actually opened, at the beginning of the process." The continuing work on Argonaute exemplifies how the lab rarely stops after solving a structure. "Often the structure informs genetic and biochemical studies that enable us to learn how a particular biological process works," she says.

Collaborative leader

As her career in research has progressed, Joshua-Tor has come to appreciate the importance of being flexible—ready to take on new challenges. A decade ago she became passionately engaged in efforts to help find a solution for malaria, investigating structures that might yield targets for new drugs. In the last several years, her lab has been motivated to study a class of enzymes called TUTases, which are promising targets for new cancer therapies. Joshua-Tor also collaborates with Bruce Stillman to solve



Crystals are highly regular, repeating structures, and when x-rays are shot through them, the particles are diffracted as they bend around the edges of their flat, angled surfaces. The resulting pattern is analyzed with computers to ascertain the exact shape of the crystallized subject—proteins or nucleic acids.

The control center for CSHL's cryo-electron microscope [see cover image for a view of the powerful machine].

mysteries about the human Origin Replication Complex (ORC), the "initiation protein" for DNA replication, which Stillman's team discovered, in yeast, in 1992.

Joshua-Tor is proud of her role in helping to launch the Ph.D. program of the Watson School, which accepted its first students in 1999. She and others, including founding dean Winship Herr and Bruce Stillman, agreed that it was important to design a flexible graduate program. "In science, you always have to be willing to rethink," she says. "We apply this philosophy to the school." At an early point in her own graduate education, a rotation to a structural biology lab opened her eyes to new possibilities. She thinks all students should have multiple chances to discover their passion.

As she and Hannon had collaborated on Argonaute, they joined forces again—with others including Stillman, Herr, Michael Hengartner, Scott Lowe, and Bill Tansey—in helping to build a curriculum for Watson School students. From 2007 to 2012 Joshua-Tor served as Dean, while Hannon chaired the admissions committee. "We were very much partners in running the school," she says. "The partnership with Greg was one of the most important I've had at the lab, both in science and at the school."

This was the very first class taught at the Watson School—a lecture by Joshua-Tor on structural biology. Before putting on 3D glasses, she read to the students a passage from Francis Crick's autobiography: "Almost all aspects of life are engineered at the molecular level, and without understanding molecules we can only have a very sketchy understanding of life itself. All approaches at a higher level are suspect until confirmed at the molecular level." These words, says Joshua-Tor "are the basis for all biology. They are the basis of my life—words I live by."

The U.S. Department of Energy's National Synchrotron Light Source at the Brookhaven National Laboratory.

The year after being named Dean, Joshua-Tor was selected to join the elite ranks of HHMI Investigators, a distinction she continues to enjoy that she says has given her great freedom as a researcher. In addition to advising and at times leading committees that have managed the National Synchrotron Light Source at Brookhaven National Laboratory, she has served on advisory panels on the future of structural biology and on the biomedical workforce for the National Institutes of Health.

As her accomplishments have accumulated steadily, it follows that Joshua-Tor has been regarded by colleagues and students as a leader—not only an academic and research leader, but also as a mentor for women trying to succeed in science. She accepted an invitation to be faculty advisor for the Women in Science and Engineering (WISE) group when it formed on campus in 2015.

Joshua-Tor is sensitive to the special challenges women face in scientific careers. "When I grew up in science, there was an image of what a woman-scientist looked like, and how she carried herself," she says. "I remember being told, early in my career, that 'they're not going to take you seriously' if I didn't conform to this image."

Joshua-Tor helped develop CSHL's innovative Ph.D. program and served as its Dean.

She concluded that such advice, though troubling, was dispensed by people who were trying to help. Over time, she says, "I learned I had to do things in a way I was comfortable with, to be who I am. I tried not to be too conscious of the 'woman' thing, although today I'm thinking about it and doing more about it than ever before. I don't want to drop it. It's important."

Three years ago, in remarks made upon accepting the Women in Science and Education Leadership Award, given by the ACE Women's Network, Joshua-Tor quipped: "Two plus two equals four—even in pink." She says she is grateful for the attentiveness of Bruce Stillman and COO Dill Ayres to "thinking about issues of concern to women scientists and how we can make things better." At the moment, however, she, like many of her colleagues, is focused on another issue: figuring out ways to make sure "the people of our country understand how important the public investment in science is." That's an issue that touches the very heart of the scientific enterprise, to which Joshua-Tor has devoted her career.

Peter Tarr

Faculty & Friends

Toasting serendipity

Four decades ago, scientists made a discovery that "completely transformed all of biology," according to Nobelist James Watson. Two leaders of the research had spent their early years at CSHL. In 1977, Phillip Sharp (then at MIT) and Richard Roberts (at CSHL) independently discovered RNA splicing. The game changer was the realization that information encoded in the DNA of our genes and copied into molecules of RNA has to be edited—spliced—before it can be used by our cells to direct protein synthesis. It was a completely unexpected discovery that won them the Nobel Prize in 1993. It was, says Roberts, the product of raw curiosity, years of persistent experimentation, and just a dash of "pure serendipity."

Five Nobelists participated in the anniversary meeting and shared a toast with Yale Professor Joan Steitz (second from the right). Nobel Prize winners from left to right: Phil Sharp (1993), Michael Rosbash (2017), Tom Cech (1989), Walter Gilbert (1980), and Rich Roberts (1993).

Splicing helps explain the astonishing diversity of human proteins. It's also a source of error in many genetic illnesses. Its discovery was a classic instance of basic research paying off. "If all you do is focus on some goal at the far end, and try to make it into a straight line," Roberts says, "you're almost guaranteed to miss all the little interesting sidelines that will lead to true discovery!" It took 40 years from the discovery of splicing to the development of a therapeutic that manipulates the splicing process to make a protein that helps children overcome a deadly disease known as Spinal Muscular Atrophy. Learn more in our special interactive feature @ labdish.cshl.edu/sma

In October, CSHL celebrated the scientists and the continuing evolution of knowledge about splicing with a scientific meeting: **Forty Years of mRNA Splicing: From Discovery to Therapeutics**. It was the eleventh in a series organized by the CSHL Meetings & Courses Program together with the Genentech Center for the History of Molecular Biology and Biotechnology. Visit library.cshl.edu for more about all of the meetings.

Light, cryptochromes, action...

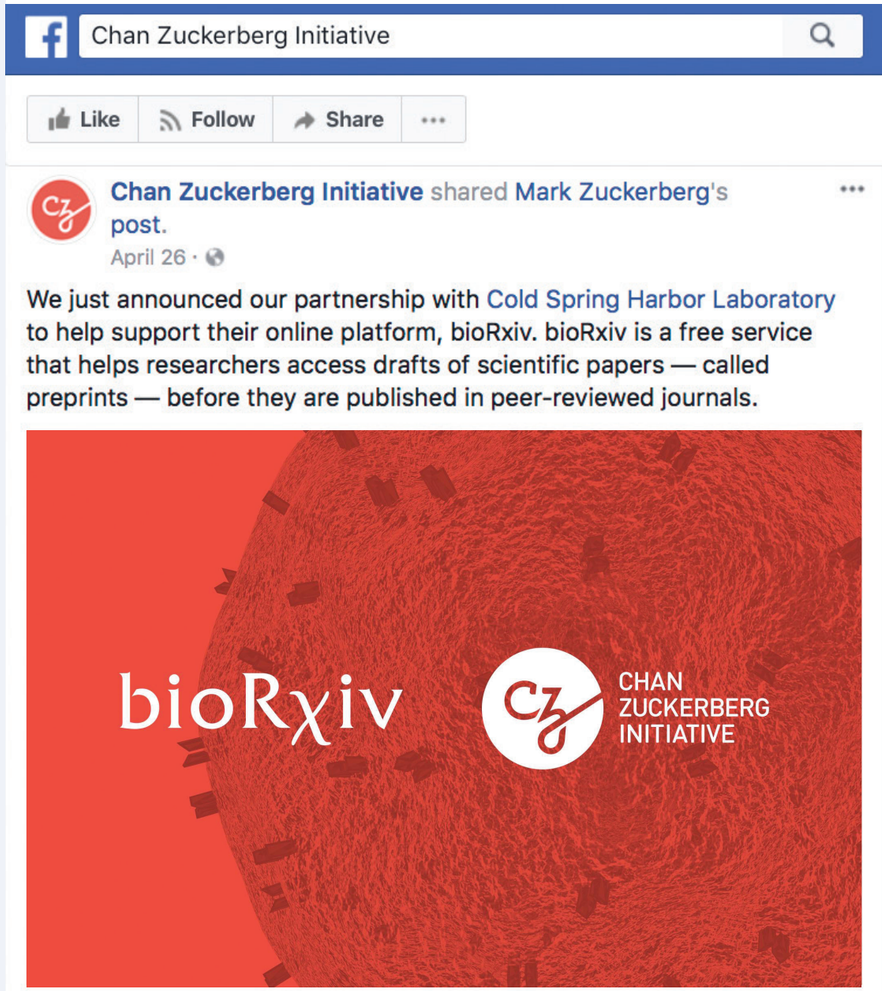
Assistant Professor Ullas Pedmale has received the National Institutes of Health "Outstanding Investigator Award," a 5-year grant in recognition of "a record of research productivity with unusual potential." One of only two plant biologists awarded, Pedmale studies how the environment of an organism regulates its growth and development. Without a brain, plants successfully integrate internal and external signals and make appropriate decisions about growth. Light is a key external signal because it drives photosynthesis and provides information about the local growth environment, including diurnal and seasonal time. To understand the molecular mechanisms by which a plant perceives and responds to its light environment, his lab will focus on cryptochromes (CRYs), the interface between the light environment and an organism. CRYs are present in diverse organisms including humans, where they regulate circadian rhythms, several physiological processes, and diseases. Pedmale hopes his work will help to improve crop productivity and to develop optogenetic tools to target neuronal disorders. In humans, disruption of CRY activity is associated with many disorders including cancer, inflammation, insomnia and diabetes.

Additional brain power

For neuroscientists, the brain presents an almost endless number of mysteries to be solved. Assistant Professor Tatiana Engel, the newest addition to CSHL's Swartz Center for Computational Neuroscience, is focused on the dynamics of neural circuits. She wants to understand the role of changing neural activity patterns in decision-making and attention.

While earning her doctorate in Physics at Humboldt University in Germany, Engel became interested in computational neuroscience. She welcomed the ability to use mathematical tools, like the analysis of complex systems, for real-life applications. Recruited to CSHL from Stanford University's Howard Hughes Medical Institute, where she was a Research Scientist, Engel is now working on a new way to analyze large-scale neural recordings, in which signals from many neurons, throughout the brain, are collected as animals perform a variety of tasks.

She looks forward to helping establish consensus among the scientific community on how to process the copious amount of data such experiments generate.



Faculty & Friends

Hungry for science

The 12th annual Women's Partnership for Science luncheon celebrated honorary director of the CSHL Association Freddie Staller. "Freddie brings a lot of enthusiasm in everything she commits to helping, all of the organizations she supports, including the Laboratory," said CSHL President Bruce Stillman, noting both Freddie and her husband Erwin's generous contributions throughout Long Island.

The featured speaker was Sarah Diermeier, a senior fellow in the lab of Professor and Director of Research David Spector. Her presentation, "Attacking Metastatic Breast Cancer with Dark Matter," described how little-explored regions of the genome could reveal new treatment opportunities. A drug targeting this genomic "dark matter" dramatically reduced breast cancer metastasis in laboratory tests, and the Spector lab hopes to get the treatment into clinical trials soon.

Luncheon guests topped 250 this year, reaffirming a growing appetite in the community for information from scientists about the latest developments in biology.

Raising over $2 million over the years in honor of women in science, we congratulate the 2017 co-chairs: Elizabeth Ainslie, Barbara Amonson, Lori Bahnik, Michele Celestino, Susan Cohen, Janet DellaFera, Diane Fagiola, Carolyn Gero, Kimberly Griffiths-Broder, Virginia Knott, Anita Lamb (Jefferson Family Charitable Foundation), Amanda Lister, Smadar Maduel-Chaluts, Stand Up For Suzanne, Mickie Nagel, Jamie C. Nicholls, Kristin Olson, Pat Petersen, Daniel Gale, Whitney Posillico, Lonnie Shoff, Dr. Marilyn Simons, Freddie Staller, Cynthia Stebbins, Mary Striano, Marjorie van de Stouwe, M.D., and Heather Warren-Whitman. Find out more about the CSHL Association and how you can participate at cshl.edu

Welcome back, Dr. Myat

Monn Monn Myat, Ph.D., is the new Associate Dean of the Watson School of Biological Sciences. But she is not new to CSHL. In 1990, as a sophomore at Mount Holyoke College, Myat was selected for the Lab's summer Undergraduate Research Program. Inspired by the research under the mentorship of Professor Adrian Krainer, she graduated early in order to pursue a Ph.D. at the Rockefeller University. The focus of her research was cell migration, which led to work for over a decade at Weill Medical College of Cornell University—where she earned several research awards, including the American Cancer Society Research Scholar Award. It was there that she discovered the passion for teaching and interacting with students, which she continued to do at Medgar Evers College until returning to CSHL this year.

Double Helix Medals dinner

The 2017 Double Helix Medals were presented on November 15 to Tom Brokaw, journalist and spokesperson for Multiple Myeloma Research and Helen Ann and Charles Dolan, advocates for cancer research.

Thanks to the leadership of the event and an anonymous donor who has matched the proceeds, CSHL raised more than $4.5 million that night. We applaud event chairmen: Jamie Nicholls & O. Francis Biondi; Mr. & Mrs. Stephen B. Burke; Kate Medina & Leo Guthart; Mr. & Mrs. Robert D. Lindsay; Mr. Thomas M. Rutledge; Mr. Joshua Sapan; Mr. & Mrs. Paul Taubman; and Charles B. Wang & Nancy Li.

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.

Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

cshl.edu goes mobile

Visit www.cshl.edu to sign up for our monthly email newsletter.

Keep up with the latest research and education advances wherever you go!

The upgraded website enables you to explore the Lab on your smart phone, tablet or desktop.