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High-yield agriculture

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A century of plant genetics at CSHL seeds new approaches

HARBOR

TRANSCRIPT





PRESIDENT'S MESSAGE

Our history began 120 years ago. The basic research in the fields of biology and genetics that has been conducted at CSHL over these many years has had a profound impact on society. Our research has started revolutions in medicine and agriculture, and is now helping to launch one in alternative energy production. Our education programs have prepared science students and teachers to understand the latest developments in biological research. Our passion for science has never been stronger.

The Harbor Transcript shares our passion with a broader public audience. It provides us with an opportunity to celebrate the people who make science happen passionate people with ideas and the desire to put those ideas to the test. In this issue, you get a real sense of the impact of our people past, present and future. This could not be more poignantly portrayed than in our article about a quest to improve agriculture that began with George Shull's important work in 1908. That quest continues with the resounding success of our plant biologists in new research that promises to improve food production.

I also invite you to read in these pages about my own laboratory, which started at CSHL over 30 years ago. Then, I was a 25-year-old postdoctoral student looking for the best place in the world to start my career. Over these decades, CSHL has made seminal discoveries in basic biology that have led to important innovations and improvements in cancer diagnosis and therapeutics.

We are proud of the CSHL legacy and the fact that our past successes have been largely attributable to the bright young minds that this institution has historically recruited. This year we've added five new faculty whom we introduce here. Think of them as our latest investment in the future.

In marking the milestone of 120 years, I thank you for supporting the people of CSHL whose unrelenting enthusiasm for science will continue to define our leadership in years to come at the frontiers of discovery in biology.

Brue Libleman

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Assistant Professor Zachary Lippman seeks to identify the genetic basis of heterosis, the phenomenon that allows hybrid plants — in this case, tomatoes — to achieve higher yields than their parents.



RESEARCH PROFILE

Bruce Stillman

Understanding the chromosome cycle

Bruce Stillman still speaks passionately about the subject that has been at the center of his working life for more than three decades. Ever since he began his doctoral studies, at age 22, he has been trying to learn more about how multiplying cells make precise copies of their genetic material.

"Just imagine," he says. "In almost every one of our cells — the approximately 100 trillion cells that make up the organs and tissues of the human body — we've got 23 pairs of chromosomes, one set from each parent. Postdoc Anthony Mazurek and graduate student Marlies Rossmann in the lab with their mentor.

So each time a cell divides, six billion base-pairs of genetic information within the six feet of DNA in our chromosomes have to be copied, precisely. Try to imagine tiny machines copying this information, different parts of which accurately read and copy each bit of the double helix, and at the same time edit the copies for errors. It's an absolutely extraordinary process."

Stillman's career in research, which has continued without interruption throughout the years he has been Director and President of Cold Spring Harbor Laboratory, has been full of discoveries about a portion of the replication machinery. He is interested in the chromosome cycle, the series of exquisitely timed processes and mechanisms by which chromosomes are duplicated and then segregate themselves in cells that are preparing to divide.

The study of how chromosomes are copied is an excellent example of basic science — it is one of the predicates upon which advances in the treatment of serious disease is based. Cancer, for instance, is a disease of uncontrolled cellular proliferation; surely we must understand the exact mechanisms used by cells to proliferate if we are to achieve better results in our efforts to fight cancer. Replication of the genetic material, and errors and defects that occasionally crop up in the process — some of which can set cells on a malignant course — are therefore of acute interest.

For 18 years Stillman has headed CSHL's National Cancer Institute-designated Cancer Center. Yet to regard him strictly as a cancer researcher would be to miss something important about both basic science and his career. For he did not set out at age 22 to understand cancer, but rather, the rudiments of the replication machinery that are active in every eukaryotic cell — the nucleated cells of higher organisms. "As I have counseled my students, it is important to work on problems that are fundamental in biology. But as I also like to say, there are lots of unintended consequences in science — you never know where the work is going to take you. And therein lies much of its value."



Replication's exquisite choreography

The attachment of ORC (origin recognition complex) at the replication start site is the first step in the assembly of a complex called the pre-RC (pre-replication complex). Stillman's team has been in on all of the major discoveries: the recruitment by ORC of two proteins, Cdc6 and Cdt1, which in turn load a third and structurally more elaborate protein, the Mcm complex, also known as helicase. Arrayed adjacent to ORC, these barrel-shaped enzymes are poised to unwind a segment of the double helix, thus creating a replication fork — the opening step of the DNA copying process. In every iteration of the cell cycle, pre-RCs assemble at every origin site on the genome. (This is called licensing.) Although many thousands "fire" during any given replication, not every pre-RC fires every time. Those that do fire must collectively make one and only one copy of chromosomal DNA.



Captivated by tumor viruses

Stillman, who grew up in Melbourne, Australia, was an undergraduate at the University of Sydney in the period when recombinant DNA was developed. This was also when work on viruses that cause cancer was advancing. "One of my Sydney professors took a sabbatical year at Stanford and I received letters from him saying, 'You wouldn't believe what's going on here.'" Stillman was hooked. He applied and was accepted at the John Curtain School of Medical Research at Australian National University, where he devoted himself to the study of human adenovirus, one of a number of very simple viruses that causes cancer in animals and helped teach scientists some of the secrets of DNA replication.

Stillman's work fit right in at Cold Spring Harbor Laboratory, where he arrived in 1979 to do postdoctoral research. Two important figures in molecular biology, both British and both associated with Stillman's Australian graduate school, were affiliated with the Laboratory: former Director John Cairns, famous for his work on replication of the bacterial genome; and former CSHL Assistant Director Joseph Sambrook, a pioneer in the study of DNA tumor viruses. In the early '80s Stillman, by this time running his own lab, began studying the biochemistry of another very simple virus, a tumor virus called SV40. The SV40 genome was a wonderful target for research: a small, double-stranded circle of DNA, which became exposed once the virus penetrated the membrane of cells it attacked.

"An experiment done in 1978 here at CSHL by Bob Tjian [now president of the Howard Hughes Medical Institute] was very interesting to me," Stillman remembers. "He had purified a protein called T antigen that was encoded by the SV40 genome." When T antigen was injected into cultured human cells, the cells started duplicating their DNA. What particularly intrigued Stillman was the fact that T antigen was known to be an oncoprotein — a protein encoded by an oncogene, a cancer-promoting gene. The notion of a protein somehow initiating DNA replication would be something Stillman would study in great detail in the years to come.

Over the next decade, his lab and a few others in the U.S. used a technique called fractionation to pick apart the elements that enabled SV40 to replicate its tiny genome in host cells. This painstaking process involved isolating and then purifying a number of individual proteins. "Eventually we were able to reconstitute the

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replication of the entire SV40 genome in a test tube, using the proteins we had purified."

The next logical step was to apply the same approach to replication of the genome in eukaryotic cells, cells that contain a nucleus full of DNA, such as our own cells. Stillman turned to yeast, a single-celled eukaryote, and succeeded in identifying many of the same proteins he had found in the SV40 replication system. All of the proteins except one turned out to be present in human

It is in the very nature of science that the more we find out, the more we realize we don't know. Therefore we continue to explore.

Bruce Stillman, Ph.D.

cells. The exception was the virus-encoded T antigen the protein that had the very specific role of attaching itself to the double helix and starting the replication process in SV40-infected cells. Not only did it recognize the "origin of replication" in virus DNA; T antigen was also shown by Stillman's group and several others to be central in the unwinding of the double helix - a necessary prelude to the bidirectional copying of each DNA "template" strand and in the recruitment of

proteins to the replication start site. These proteins were the building blocks of the molecular machinery that actually synthesized new genetic material.

Stillman was convinced that there was something like T antigen in eukaryotic cells. This was controversial. "There was evidence that there were *no* specific start sites for copying DNA in eukaryotic cells, implying that they lacked a specific start protein. I never liked the idea. The problem was, if the process was random, how could you insure that the all the DNA in chromosomes was copied *once and only once* per cell cycle?"

This reduced to the question of how chromosomal replication was regulated in nucleated cells, which, unlike simple bacteria, had *multiple* replication start sites. (The yeast genome, it turned out, has about 300 origins — specific sequences in its DNA from which replication proceeds; in the human genome, we now know, there are more than 30,000 origins.) Stillman strongly believed that in the evolution of complex cells and organisms, very fine control mechanisms had to have emerged, in order to protect the integrity of the chromosomes as they were duplicated and segregated into "daughter" cells during the process of cell division.

ORC – a landmark discovery

Stillman was vindicated after years of hard work. In May 1992, he and then-postdoc Stephen Bell published a landmark paper in *Nature* in which they described their discovery of a multi-protein complex that recognized and bound to specific DNA sequences in yeast that were the start sites for copying DNA. They called this molecular machine ORC, for origin recognition complex. As subsequent work would show, just as ORC was the "initiation protein" for DNA replication in yeast, so its analogs would perform this crucial role in all other organisms, including humans [see box, p. 3].

ORC in humans, and indeed the entire process of DNA replication in human cells, is "much more complex" than in yeast, Stillman notes. Implicit in that statement are the gleanings of nearly 20 additional years of basic research, work that continues in Stillman's lab to this day — and, much to his pride, in the labs of several of his former students and postdocs, notably Steve Bell, John Diffley and others. In 1992, they scarcely knew how pervasive a role ORC and related proteins would prove to have in the chromosome cycle, a fact with interesting evolutionary implications.

Take for example the questions of redundancy and timing. There are thousands of replication start sites along each linear human chromosome. Why so many? What determines when and how they fire? The great number of sites can be attributed to the need of replicating a large genome rapidly — within a defined period in the cell division cycle. As for the number of sites, "They tend to fire in little clusters, some earlier and some later during the DNA synthesis 'S'-phase," Stillman says. "That has got to do, in part, with the way the genetic material is packaged in the nucleus." One unexpected finding was that ORC could participate in the organization of the structure of chromosomes and hence influence the expression of genes as well as when during S phase chromosomes are copied.

Much more recently, components of the ORC complex have been found by Stillman and colleagues to be involved in duplication of material that insures proper chromosome segregation during the part of the cell cycle called mitosis, when chromosomes segregate before a cell divides into two daughter cells, each





ORC and the chromosome cycle

In cells of higher organisms ORC is a complex of six proteins whose diverse functions were not anticipated when ORC was discovered in yeast in 1992. In this series of images made by Stillman's team, we see cells at 4 distinct moments in one full cell cycle at which ORC plays roles related to chromosome replication and separation (the "chromosome cycle"). In the G1 (Gap1) phase of the cell cycle (1), ORC binds to sequence-specific origin sites across the genome and recruits other proteins to form the pre-replication complex [see box, p. 3]. After a given origin fires in S (synthesis) phase, various ORC subunits help regulate chromosome assembly and separation. In the M (mitosis) phase of the cell cycle: (2) ORC subunits localize to centrosomes, and the Orc1 subunit is involved in control of duplication of centrioles; (3) Orc2 and Orc3 subunits are required for stable attachment of the spindle, the structure that separates "sister" sets of chromosomes during cell division; (4) Orc6 is required for cytokinesis, the division of the cytoplasm into two daughter cells; it binds proteins essential to the process called septins.

containing one full set of chromosomes. "We published a paper in *Science* last year that shows how ORC controls duplication of the centrosome" — an organelle in cells that organizes the spindles that pull the duplicated chromosomes into two equal sets just prior to cell division; "and we have just submitted a paper showing that ORC is required for proper function of the centromere" — the region in each of the duplicated chromosomes that is tethered to the spindles so that they segregate correctly to the daughter cells.

Why would ORC be involved? "In evolutionary terms, my guess is that ORC is a chromosome-organization protein," Stillman says. "When the first chromosomes acquired the ability to control when they duplicate and how they segregate, the origins — the replication start sites — would logically be linked to sites on the genome where the chromosomes would be pulled apart." In trying to sum up a long and productive career, Stillman is philosophical. "We certainly have a good sense, now, of how the genome is copied. When I first started out we didn't have a clue. But it is in the very nature of science, of course, that the more you find out, the more you realize you don't know. So the process continues, and we continue to explore." For example, many of the proteins his lab discovered are also involved in processes that repair DNA when it is damaged by chemicals or UV light, and some are involved in the signal processes that arrest cell proliferation if the genome is damaged, biochemical steps that are lost in all cancer cells.

Stillman's body of work is a superb example of the reason our society invests great sums each year in fundamental science. For as he points out, no one can know where the process leads — "and therein lies its unique value." **Peter Tarr**

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Scholar's oasis

In June, members of the Cold Spring Harbor Laboratory community celebrated the completion of an expansion and renovation of the venerable Carnegie Building, which dates to the institution's infancy in 1905. In addition to a new state-of-the-art climate-controlled vault for storage of precious archival collections that trace the history of molecular biology and genetics, and a number of beautifully appointed expanded reading and study rooms, the updated Carnegie Building now also boasts an Annex, named for CSHL alumnus and longtime Library & Archives benefactor Waclaw Szybalski, Ph.D. The jewel of the Annex is without question the Szybalski Room, pictured here. (Its namesake's portrait can be seen hanging on the north wall.) The room's generous proportions, vaulted ceiling, and gracious arched windows - which fill it with an inviting, warm light - will surely make this a favored spot on the campus to read, reflect, or meet with colleagues. Peter Tarr

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One experiment

Deep brain stimulation (DBS)—which involves shooting steady pulses of electricity through slender, implanted electrodes—acts like a pacemaker in the brain. It greatly reduces the tremors, stiffness and movement problems that are characteristic of Parkinson's disease, and works against other brain disorders such as epilepsy and severe depression, as well. CSHL's Dr. Grigori Enikolopov recently teamed up with neurosurgeons in Canada to examine the effect of DBS on the hippocampus—the brain's control center for spatial and long-term memory, emotion, behavior and other functions that go awry in these diseases.

Enikolopov's group developed new mouse models in which neural stem and progenitor cells in the adult brain produce a fluorescent color. This enabled the scientists to visually track these cell populations and quantitatively assess how they change in response to neuronal triggers such as DBS.

In one experiment, Enikolopov and his collaborators stimulated an area in the mouse brain equivalent to a human brain area where DBS is therapeutically applied. The result was an increase in the number of new neurons due to an increase in cell division in the hippocampus, specifically among neural stem and progenitor cells (seen as red dots). More primitive stem cells are also identified by their green radial strands. Interestingly, these same populations are known to increase in number following physical exercise and treatment with antidepressants such as Prozac. The team's analysis suggests that the tracking of new cell growth in the hippocampus could help pinpoint the sites at which therapeutic DBS (or other stimuli) might work best for various neurological and psychiatric conditions. **Hema Bashyam**

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High-yield agriculture

A century of plant genetics at CSHL seeds new approaches



In the summer of 1905, on a small patch of land next to what is now the Carnegie Building at Cold Spring Harbor Laboratory, a 31-year old scientist named George Shull began to grow maize, or corn, in a series of experiments that would change the face of modern agriculture. This year, CSHL scientists made two fundamental discoveries that continue the legacy at the Laboratory that began with Shull to improve the world's food supply.

Soon after completing his doctoral thesis at the University of Chicago, Shull had taken charge of plant research at the Station for Experimental Evolution, one of two Long Island institutions that would merge half a century later to form CSHL. His goal had been to publish experimental support for Charles Darwin's theories of evolution. But what he actually accomplished had an even greater impact. Based on one of Darwin's ideas, he devised a practical solution to boost agricultural productivity.

A dormant idea feeds a hungry world

In 1876, Darwin wrote of a curious phenomenon, hybrid vigor, or heterosis, to describe his finding that the hybrid offspring of cross-pollinated plants grew much taller than the inbred offspring of self-pollinated plants. The idea remained latent, however, until Shull followed up on it 30 years later.

Self-pollinating a corn plant for generations, Shull found, resulted in inbred offspring that got progressively smaller in each generation, producing smaller corncobs with fewer seeds. But when Shull inter-crossed two such poorly yielding varieties, the hybrid progeny spectacularly outperformed their parents in growth and yield.

Shull realized that his initial regimen of inbreeding had separated a genetically diverse corn plant into an array of "pure" lines, which could then be "crossed" to produce vigorous hybrids. Here then was a way to increase crop yield, a goal that corn breeders had been pursuing for thousands of years. In a 1908 paper titled "A pure-line method for corn breeding," Shull modestly wrote, this "method ... may perhaps give results worth striving for."

It did, and in the most profound way imaginable. By the 1930s, most farms in America were using Shull's method to grow high-yield corn. This method significantly contributed to the war effort and the rehabilitation of postwar Europe in the late 1940s. In the last 50 years, the heterosis concept, which was successfully applied to other crops such as rice, has been the driving force behind rising agricultural yield and global food security.

Unraveling the genetics of hybrid vigor

"Ironically, though, there's still no consensus on what causes heterosis, or hybrid vigor," says plant geneticist Zachary Lippman, an assistant professor at CSHL, who is about the same age today as Shull was when he made his ground-breaking discovery. "But we are starting to identify the genes and mechanisms that drive and control it." This information will help exploit heterosis in a systematic, scientific way and maximize its benefits.



A field adjoining CSHL's Carnegie Building was the site of George Shull's corn breeding experiments in the early 1900s.

In 2004, Lippman — who had just received his doctorate from CSHL's Watson School of Biological Sciences moved to Israel to hunt for vigor-boosting genes in tomato plants. Three years later, he and his postdoctoral advisor, Professor Dani Zamir of Hebrew University, found six promising leads. While five remain uncharacterized, the sixth led to a gene that increased tomato yield by a dramatic 60%. Interestingly, the gene encodes the florigen protein, which controls when and how plants make flowers (which in turn produce fruit.)

Their discovery is the result of a novel approach that does not require technology that is currently used to produce genetically modified crops, which some find objectionable. Rather, it relies on classical breeding principles that any backyard gardener would recognize.

Lippman accepted a faculty position at CSHL in 2008. Quickly setting up operations with start-up funding from CSHL trustee Jacob Goldfield, he confirmed the "overdominant" gene's vigor-boosting power in different varieties of tomatoes. He also confirmed it in plants grown in different climates and soil conditions, such as at CSHL's own Uplands Farm and at the Cornell Horticultural Station at Riverhead, NY.

Published in early 2010, this work, which could potentially impact the billion-dollar tomato industry as well as efforts to mass-produce other flowering plants, was enthusiastically hailed by the international news media. The newspapers made much of the "the flower power gene" that could turn an average tomato plant into "a bionic fruit factory."

The gene, which boosted yield and sweetness, in fact goes by the typically subdued scientific name, *single flower truss* (*sft*). It increases yield only in hybrids that have one normal copy and one mutated copy of the gene.

"As in the Goldilocks story, there can't be too much or too little, but just the right amount of florigen to get maximum yield," explains Lippman. "A mutation in a single copy of the *sft* gene results in the exact dose, thereby driving hybrid vigor." In a spin-off project, Lippman has now joined forces with CSHL Professor David Jackson to investigate if there is such a "dose effect" that can increase yield in a major crop species such as corn.



Rob Martienssen in the lab with *Arabidopsis*, the mustard plant that served as a test-bed for his experiments with apomixis. Genetically locking in hybrid vigor

Like most cereal crops, corn reproduces sexually. For farmers, this is a disaster, as it forces them to spend an estimated \$30 billion annually on fresh stocks of qualitycontrolled seeds that will produce a uniform field of crops with a desirable trait such as high yield. Farmers can't grow these seeds themselves because sexual reproduction — the random mixing of DNA from male (sperm) and female (egg) gametes, or sex cells — will likely wipe out the very trait desired.

If Lippman's work on the genetics of heterosis points the way to superior crop yields, then the work of CSHL Professor Rob Martienssen could lead the way to locking in high yield or any other valuable trait. Then farmers wouldn't have to buy new seeds every year. Martienssen studies the biological role of mobile bits of DNA known as transposons — the "jumping genes" discovered 60 years ago by CSHL geneticist Barbara McClintock, who won the Nobel Prize for her work in 1983.

"She was really visionary," says Martienssen, who was mentored by McClintock early in his career. "In an era when none of today's genetic and genomic tools existed, she was able to conclude that transposons are important in plant development."

Martienssen's work has revealed a great deal about how transposons, which can damage DNA when they are active, are "silenced" in plant sex cells via a process known as RNA interference. Two years ago, while identifying the genes in this pathway in pollen-derived sperm cells, he made a surprising observation that genetically linked transposon silencing to a plant's ability to sexually reproduce.

His lecture about this work at the National Polytechnique Institute in Irapuato, Mexico sparked a collaboration with Jean-Phillipe Vielle-Calzada, a researcher who has spent years trying to turn sexually reproducing plants into asexual reproducers by inducing them to undergo apomixis. A

little-known trick that exists in nature, apomixis which occurs in some 350 families of plants, including the humble dandelion — essentially allows plants to make exact genetic replicas of themselves, asexually.

Early in 2010, the scientists reported results suggesting that the mustard plant — a sexual reproducer — is unable to reproduce via apomixis because of a gene called *Argonaute 9*, which is well known for its role in silencing transposons. Mutating this gene, however, unleashed transposon activity as well as the hallmarks of apomixis within the plant's reproductive organs.

"Making an apomictic high-yield hybrid is of course the ultimate goal," says Martienssen. "Then you'd never have to rely on laborious crosses again. Our work in the mustard plant was just the first step. We're still some ways off from perfecting the process to get completely viable asexual seeds and applying this to other crops."

But he's optimistic about their chances of getting there. In the summer of 2011, he and other CSHL plant geneticists will be hard at work in CSHL's fields, trying to harvest an apomictic corn plant. **Hema Bashyam**

Online: Slideshow www.cshl.edu/ Multimedia-Library/Photos

5 new faculty





- Anne Churchland 1
- Christopher Hammell 2
- Molly Hammell 3

Anne Churchland, Ph.D

Assistant Professor

Seeking knowledge about the neural correlates of cognition, Anne embarked on a path that led to CSHL via the doctoral program at UCSF and postdoctoral research in a primate lab at the University of Washington, Seattle. Last year, Tony Zador and colleagues at CSHL offered Anne the chance to test her methodology on rodents, which are far more pliable research subjects than primates. Anne came to the campus to perform preliminary experiments, but doubted they would succeed. A month later she had become a convert. "Apart from the advantages of working with rodents, I loved the atmosphere of collaboration here. In my new lab I'll be studying the circuitry underlying multimodal decision-making, in which animals - rodents gather evidence from multiple sources, for instance, aural and visual, before making a decision."



Christopher Hammell, Ph.D.

Assistant Professor

In doctoral work at Dartmouth, Chris studied mechanisms involved in nuclear export of messenger RNA. Then, as a postdoc in Victor Ambros' lab at the University of Massachusetts, he became interested in the machinery that prepares micro RNAs to target specific genes, which they in turn regulate. Chris focused on how mutations in this machinery could perturb a given miRNA's gene-regulatory activity so as to give rise to a developmental timing defect. Using C. elegans and forward genetics, he continues to follow this line of inquiry, searching for defects in genes encoding miRNAs that can set in motion a chain of events culminating in human illness.

Molly Hammell, Ph.D.

Research Assistant Professor

En route to her career in biology, Molly Hammell studied nature across its full range, from the subatomic to the extragalactic. The linkage between these disparate fields and with biology is mathematics. Molly spent five years at a wet-lab bench as a research associate in genetics and genomics under Victor Ambros at U. Mass. "I wrote algorithms that would predict what genes micro RNAs targeted; then I went to the bench, made reporters for the targets, and ran experiments to see if the prediction were accurate." At CSHL Molly is applying prediction algorithms to problems in cancer research. She is Manager of the **Bioinformatics Shared Resource.**

5 new faculty

Michael Schatz, Ph.D.

Assistant Professor

Mike Schatz comes to CSHL from the University of Maryland, where he developed methods for large-scale computational analysis of DNA sequencing data. Mike has become known for his pioneering use of cloud computing for genomics. That is, using many computers at once to work on problems that demand massive number-crunching power. "Cloud computing relies on a leasing model, so that you can rent out really impressive power for well-defined periods of time, rather than have to go out and buy it," he says. For the last several years Mike has helped run a large NSF cloud computing project, and intends to bring together several thousand available computing cores on the CSHL campus, during downtime periods, for faculty projects. Meantime, he continues with his own research in metagenomics - trying to understand individual genomes within a larger genomic context - and on genome assembly and validation projects.

4 Michael Schatz

5 Hongwu Zheng

Hongwu Zheng, Ph.D.

Assistant Professor

Hongwu Zheng comes from southwest China, where his family was relocated from the coast during the Maoist period, "in expectation of World War III!" He graduated from Sichuan University before emigrating to the U.S., where, at Boston University he earned a Ph.D. in biochemistry. Hongwu focuses on glioblastoma, a brain cancer with a poor prognosis. "We have to go down a different clinical path," he says. "We can't just keep trying the same old things again and again." He uses mice to recapitulate genetic and epigenetic aspects of the cancer, and approaches the problem from a developmental perspective. Cells have developed regulatory mechanisms over evolutionary time, to prevent aberrant proliferation. "Tumor cells devise means of self-renewing, seemingly like stem cells. We are exploring ways of restoring differentiation. If we can push tumor cells to differentiate, we might be able to stop tumor progression."





Faculty & Friends

Double Helix Medals Dinner raises more than \$3 million



Cold Spring Harbor Laboratory celebrated its fifth Double Helix Medals Dinner, an annual event initiated to honor extraordinary individuals who have benefitted human health through game-changing biomedical research or raising awareness and funds for such endeavors.

An event that has quickly become a well-attended staple of New York City's Fall roster of philanthropic events, the Dinner was chaired by Larry Norton, Amy and John Phelan, David Koch, Ron Howard, and Patricia Quick, among others. The event raised more than \$3



2010 Honorees: John F. Nash, Jr., Mary-Claire King, and Evelyn H. Lauder

million, which will serve as the financial backbone for the expansion of various research and education programs at the Laboratory.

At this year's November 9th gala, geneticist **Mary-Claire King** was honored with the Medal for Scientific Research for her outstanding contributions toward understanding the genetics of breast cancer and mental illness. One of her most significant accomplishments was her demonstration that breast cancer is inherited in some families, as the result of mutations in the gene that she named BRCA1. This discovery revolutionized the study of numerous other common inherited diseases.

The Laboratory honored **Evelyn H. Lauder** with the Medal for Corporate Philanthropy. As Founder and Chairman of the The Breast Cancer Research Foundation, Mrs. Lauder has raised over \$300 million to support clinical and translational breast cancer research conducted by over 170 scientists worldwide, including CSHL's Michael Wigler.

Nobel laureate in Economic Sciences John F. Nash was awarded the Medal for Humanitarianism for having brought worldwide awareness to and appreciation for people suffering with schizophrenia. Using his influence as a public role model, Nash has served as an effective and passionate advocate for mental health issues, pushing for the installation of both laws and programs that allow those with mental illness to lead independent and productive lives. **Hema Bashyam**

More details and images of the event can be found at http://doublehelixmedals.cshl.edu/

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Faculty & Friends

Justin Kinney named a Quantitative Biology Fellow

The Laboratory's first QB Fellow, Justin Kinney earned a doctorate in physics from Princeton, but he has spent the last two years in postdoctoral fellowships, at Princeton and at CSHL, applying his quantitative skills to biological problems. At CSHL he has worked in the labs of Bruce Stillman and Michael Zhang. His research as a Fellow will focus on the question of how sequences of very specific regions in the genome give rise to very specific biological functions. He seeks to characterize the sequence-function relationship quantitatively.

Nanomedicine retreat for 2010 President's Council

More than 60 CSHL supporters participated in the 2010 Fall President's Council retreat, an annual event hosted by CSHL President Bruce Stillman. Now in its 16th year, this weekend celebrates the CSHL Fellows Program. Participants donated more than \$25,000 to support early-career scientists in pursuit of the most promising and innovative research projects. The two-day retreat immerses these generous philanthropists in the hottest topics in science.

This year's event tackled the "The Science of Nanomedicine," with a keynote on the applications of nanotechnology in medicine by Bob Langer, David H. Koch Professor at MIT. Other experts included Harvard professor George Whitesides and University of North Carolina Chemistry Department head Joseph DiSimone.

For more information about how you can support the CSHL Fellows Program and participate in a series of educational and social events exclusive to President's Council members please contact Diane Fagiola at fagiola@cshl.edu or call 516-367-8471.



Ed Travaglianti, Leo Guthart, Marilyn H. Simons, Jamie C. Nicholls, Robert D. Lindsay, Bruce Stillman



Neuroscience program chair to pursue high-impact project

Tony Zador, Ph.D., Professor of Biology and Program Chair in Neuroscience, has been awarded a \$2.17 million, fiveyear grant by the National Institutes of Health (NIH)'s Transformative Research Projects Program (TR01). "Complex research projects, even exceptionally high-impact ones, are tough to get funded without the necessary resources to assemble teams and collect preliminary data. The TR01 awards provide a way for these high impact projects to be pursued," says NIH Director Francis S. Collins, M.D., Ph.D.

Zador's project is aimed at one of neuroscience's most fundamental, but as-yet-unknown entities: the 'connectome' or the complete wiring diagram of the brain. The brain consists of billions of neurons interconnected by trillions of synapses or junctions where electrical currents are transmitted. To understand brain function, detailed knowledge of these connections is critical. By compiling a connectivity atlas in animal models, Zador hopes to determine if and how disruption of connectivity contributes to neuropsychiatric diseases such as mental retardation, autism and schizophrenia.

See Tony Zador on www.bigthink.com.

CSHL Board Elects Jamie C. Nicholls Chairman

Jamie C. Nicholls, a former General Partner at Forstmann Little & Co., was elected Chairman of the CSHL Board of Trustees on November 6, 2010. "Her ability to translate private equity and finance experience to the non-profit academic world is a great asset to CSHL," said retiring Chairman Eduardo Mestre, Vice Chairman, Evercore Partners. The Board also elected new officers. Robert D. Lindsay, Co-Managing Partner, Lindsay Goldberg, and Marilyn H. Simons, President of The Simons Foundation, are Vice Chairs. Leo Guthart, CEO of Topspin Partners, is Treasurer and Ed Travaglianti, President of TD Bank, Long Island, is Secretary.



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CSHL Association comprises some 1,000 neighbors and friends of the Laboratory who contribute to the Annual Fund, an essential source of unrestricted support for outstanding young scientists. Association members get to know CSHL scientists at lectures, concerts, dinners and other social events that support the Laboratory. Membership levels start at \$100 per year. For more information please contact Diane Fagiola, Director of Development, at 516.367.8471 or fagiola@ cshl.edu.

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