



HARBOR TRANSCRIPT

CSH Asia

A hub for biology in Suzhou



PRESIDENT'S MESSAGE

While almost every industry today is going global in order to succeed, I would argue that basic scientific research is perhaps our most successful model of a global enterprise. It thrives on the free and open exchange of ideas, and for this reason, the best scientific research knows no political or geographic boundaries. Although scientists compete intensively among themselves — a feature of the search for new knowledge that underlies its famously rapid rate of advance — the competition cannot be contained either within disciplinary or national boundaries, any more than ideas can be. Not in the world in which we live today.

Cold Spring Harbor Laboratory's Meetings & Courses program — this year celebrating the 75th anniversary of the legendary and internationally acclaimed Symposia on Quantitative Biology — is invaluable to science because it has been from its inception a program in which scientific ideas are freely and openly shared. It is the worth of the idea, and not the professional status of the participant, that has counted above all. For these reasons, a picturesque bay on the north shore of Long Island has become a famous "home away from home" for researchers at all stages of their careers, from grad students to Nobel laureates; a place where postdocs and professors routinely challenge one another because they know that at CSHL, it's science that is paramount.

I am pleased to see the CSHL model for scientific meetings take root in Asia. At the opening ceremonies of the CSH Asia meetings program in our new facility in Suzhou this spring, we unleashed the power of intellectual freedom in a society hungry to actualize its scientific potential. CSH Asia is not CSHL "going global." It's about taking a proven concept and transplanting it, like the strong shoot of a venerable plant, in new soil. Suzhou is centrally located, proximate to the largest Chinese city, Shanghai, and within three hours by air from Tokyo, Seoul, Beijing, Taipei, and Hong Kong. Singapore (five hours) and Sydney (10 hours) are more distant, but within easy reach and a similar time zone. We expect our new facility to be a major hub at which scientists primarily from these places, but also from Europe and the Americas, meet and exchange ideas about important areas of life science, freely, openly and productively, as they do here in New York.

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On the cover:

The Suzhou Dushu Lake Conference Center provides a stylish yet informal setting for gatherings of up to 550 scientists. The cafe is shown on the cover.

CSH Asia

The “CSHL idea” takes root in China

It was a meeting that brimmed with significance for the future of science in Asia. Hundreds of people filled a sparkling new auditorium named for James D. Watson and plunged into what would be a five-day exchange of ideas about new concepts in cancer research.

The date was April 6th; the place was Suzhou, China; and any similarities the meeting bore to those in the Symposium series that Cold Spring Harbor Laboratory has made famous over the last 75 years were absolutely intentional.

The 1st James Watson Cancer Symposium, followed on April 12-17 by the equally well-attended 1st Francis Crick Neuroscience Symposium, were the historic inaugural events at the Suzhou Dushu Lake Conference Center. A fully equipped meeting place for scientists on China's rapidly modernizing southeast coast, the Center represents CSHL's most extensive effort to date to extend overseas its time-tested model of peer-organized meetings as the basis for open, critical discussion of cutting-edge ideas in biology and biomedicine.



Artist's view of Suzhou Dushu Lake Conference Center facility

The dazzling new Dushu Lake Center, whose design (see illustration, lower left) was inspired by a blending of ancient and modern in the style of I. M. Pei, a Suzhou native, is the fulfillment of an idea hatched in the back row of Grace Auditorium, half a world away from Suzhou, a few short years ago.

“I’d sit in the last row during the Cold Spring Harbor meetings, and try to take in the whole picture,” remembers Maoyen Chi, Ph.D., a native of Suzhou who worked as a computational scientist in the laboratory of CSHL Professor Mike Wigler for eight years before being named the CEO of the new meetings program in China in 2008. “I really fell in love with the academic culture of those meetings — relaxed, informal, and very free. And I began to ask myself: ‘What if we had this in China?’ What if we could build a small campus, where scientists of all levels could feel at home — maybe right near where I come from in Suzhou, where there are many beautiful mountains and lakes.”

The difference between a mere daydream and a moment of visionary insight, one might say in retrospect, is a matter of circumstance, a fortuitous alignment of forces. Little did Chi know that around the same time, David Stewart, Ph.D., the longtime executive director of the CSHL Meeting & Courses program, was having serious thoughts of his own, not specifically about China but about CSHL's role in Asia.

A Model of Openness

“For a number of years, people had been coming to us and asking us to get involved in Asia,” says Stewart. “There were complications of various kinds. What I knew, though, was this: we had a fantastic program at CSHL, admired the world over; and we have never been in the habit of standing still.” Since 2001, Stewart has been instrumental in establishing a joint program with England's Wellcome Trust, to create a meetings program in Cambridge modeled after CSHL's. Now the question was on what basis to bring the CSHL idea to Asia.

Stewart and President Bruce Stillman agreed about the major points. “Bruce felt strongly that total independence was the key. If we joined forces with a scientific society or state-organized scientific operation, it would likely have its own agenda; it would likely be intended as a spotlight for a single nation's scientists. That's not what we



Suzhou: bounding into the future while preserving an ancient past

The Dushu Lake Conference Center, like the high-tech “industrial park,” is something brand new at the edge of something very old and deeply venerated. The 10-square-mile Suzhou Industrial Park is just east of the old city of Suzhou, whose origins (and ancient city wall) have been traced to a time 2500 years ago, during the late Shang Dynasty. Despite the enormous growth in southeastern China in recent decades, Suzhou’s old town has been preserved, recognized the world over as a treasured cultural site. The city has long been among China’s most prosperous. Its location in the Yangtze River basin and along the path of China’s ancient Great Canal made it a center of commerce, including an important outpost of the silk trade. The city’s peerless gardens, framed by “moon-gates” (pictured above) that have been used as an important architectural motif in the Dushu Lake Conference Center, are among the World Heritage Sites listed by UNESCO. These classical gardens



were built by gentry during the Ming and Qing dynasties, and are a “must-see” for scientists attending meetings at the Center. The old city is equally famous for its canals and thousand stone bridges, which account for references to Suzhou as “the Venice of the East.” It is Suzhou’s ultramodern “satellite cities,” built on the periphery of the ancient town, that account for its present economic dynamism.

wanted at all. One of the things that makes Cold Spring Harbor Laboratory such an important force in science is its independence.”

Stewart was motivated by positive feedback he had received over many years from Asian scientists attending CSHL meetings. Like Maoyen Chi, many of them singled out the feeling of openness and camaraderie that they fostered. “The CSHL meetings offer scientists an opportunity to present their own work and get it critiqued, through immediate feedback from colleagues. This is incredibly valuable,” Stewart notes. “Our meetings are also famously democratic — people with decades of experience in their field can be challenged by grad students and postdocs. Our effort to involve young scientists in particular provides a powerful model, different from but complementary to the traditional, top-down model of scientific communication.”

A plan to take this idea to Asia came together with surprising speed in the summer and fall of 2006. In

August, Stewart and Chi met for a beer at the Blackford bar, some months after Stewart’s return from an exploratory trip. Chi shared his dream of locating a state-of-the-art meeting center near his native Suzhou, a 2500-year-old city of 6 million people located about 40 minutes inland by high-speed train from the coastal megacity (and traditional Chinese economic capital) of Shanghai, population 20 million. Chi had contacts in Suzhou whom he had reason to believe might welcome a CSHL-run meeting center.

Within the month, Chi and Chinese officials representing a sprawling development called the Suzhou Industrial Park, or SIP, were able to agree on the broad outlines of a plan. Bruce Stillman and Jim Watson thought well of it. In October 2006, Watson accompanied Chi to Suzhou to meet the SIP leadership. “Jim’s a huge figure in China, and I think the idea really captured his imagination,” says Stewart. “I liked the idea,” Watson says today, “because it is important that we know the best scientists in China and throughout Asia. We want to have exchanges with

them, including a role in training their postdocs. We can play a part in bringing young people in Asia to the frontiers of science."

By November 2006, an agreement of understanding had been signed. Stillman regards it as a good example of the Laboratory's "scientific entrepreneurialism," a means of propagating a democratic model of scientific exchange in a part of the world where science is growing faster than anywhere else. (see "An Asian hub," p.5)

SIP, which is no mere American-style "industrial park" but rather a burgeoning high-tech city of 300,000 built from the ground up over the last decade, agreed to finance construction of a conference center, stylish hotel accommodations and a grand ballroom, all accommodating 550 guests; an exhibition space for up to 300 posters; separate seminar rooms where breakout sessions as well as Banbury-style small meetings could be held; and a fabulous octagonal-shaped bar/restaurant — a social hub for the complex — projecting out into Dushu Lake. SIP, which is funded jointly by the Chinese and Singapore governments, provided CSHL with \$9 million in startup funds. In exchange for this sum, CSHL agreed



Lobby of Dushu Lake Convention Center

to create and manage a meetings and courses program for the new facility, a program CSHL wholly owns and has complete freedom in directing.

Both Stewart, who is president of CSH Asia, the CSHL subsidiary that owns the Suzhou meetings and courses program, and Chi, its CEO, are keen to stress, in Stewart's words, that "the program is not a U.S.-Chinese bilateral partnership." As Chi puts the case, "We call ourselves CSH Asia, and what that signals is our aim of making a home for scientists throughout Asia which happens to be situated in Suzhou."



The 550-seat James Watson Auditorium

The facility has space for 300 posters



It is “every bit as important to us,” says Chi, that scientists from Japan, Korea, Taiwan, Hong Kong, Singapore, and Australia regularly attend meetings at the Dushu Lake Center “as scientists from the Chinese mainland.” He points out (see map, below) that Suzhou is a two- to three-hour plane ride from all of those places, save Australia and Singapore, which are, respectively, five and 10 hours distant by air. “The idea,” Chi says, “is to make a hub for biology, a pan-Asian hub, where the Cold Spring Harbor Laboratory way of doing meetings — the scientific rigor plus the openness and informality, set against a backdrop of great natural beauty — makes Suzhou Dushu Lake a place scientists will want to come back to year after year, just as thousands of scientists make the annual pilgrimage to CSHL.” **Peter Tarr**



A swimming pool is one of many recreational features of the Center.



An Asian hub

From virtually a standing start, mainland China has rocketed over the last decade into the ranks of the world's leading producers of scientific and technical knowledge. In the life sciences, China's performance on a relative basis outstrips that of any other nation, based on a PubMed search: its scientists are publishing peer-reviewed papers in English at an average annual growth rate that has exceeded 10% since the year 2000, vs. less than 1.8% for the U.S. Interestingly, the five fastest “growers” for the period are all in the South Asia/Asia-Pacific region, the remaining four being South Korea (9.4%), India (7.5%), Taiwan (6.2%) and Australia. All of the cities shown in the map, right, are within three hours by air of Suzhou; Singapore and Sydney are five and 10 hours away, respectively.



Molecules of memory

Revelations about memory's mechanisms with implications for Alzheimer's and other illnesses

Those who have been following news about brain research over the last year should have no trouble remembering the name Yi Zhong. Three times since last October, Zhong, a professor at Cold Spring Harbor Laboratory, has published headline-grabbing research papers explaining at the level of individual molecules some of the mysteries about why we remember and forget things.

In this and related work, Zhong, along with colleagues at CSHL and in China, are not only adding to our fundamental understanding of the brain; they are progressing steadily along a path that could culminate in treatments for a range of serious illnesses involving memory impairment, from mental retardation to Alzheimer's disease.

Like others who have come before him, Zhong uses the fly as a comparatively simple model with which to study both the genetics and cell biology of neurons *in vivo* — in living, “behaving” animals. Because of a phenomenon called sequence conservation, many of the key genes in the fly brain involved in memory and learning have been preserved across eons of evolutionary history — so useful have they proven for survival — and have close cousins in the brains of mammals, including man. Improbable though it may seem, therefore, one can learn about the human brain by looking closely at the fly brain.

Zhong's approach is distinctive. Rather than beginning with the fly and working toward man, “we begin with the human being, and by this I mean working with the genes of people who are sick,” he explains. Zhong looks for gene mutations known to cause nervous-system illness in humans, such as *NF1*, linked with neurofibromatosis. People with an *NF1* mutation — often inherited from a parent — can suffer learning defects and develop neurofibromas, tumors that split apart nerve fibers.

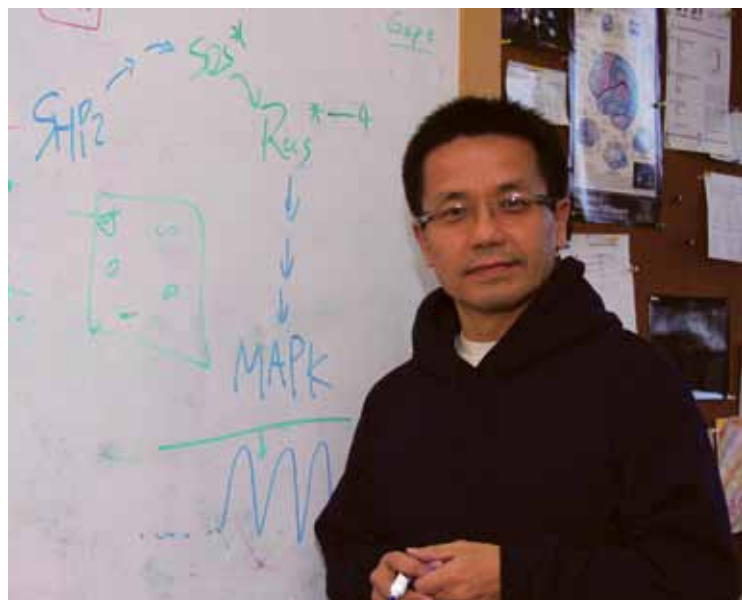
From a human gene known to cause trouble when mutated, Zhong moves to the fly. In neurofibroma, he was able to show how *NF1* mutations in fruit flies affect a pathway critical for learning. His team also discovered that *NF1* and another gene, called *corkscrew*, in the same biochemical pathway, also play a critical role in memory. That insight is pertinent in an illness called Noonan's syndrome. Noonan's causes characteristic facial malformations as well as deficiencies in long-term memory. It's fairly common, occurring with about the same frequency as Down syndrome.

Noonan's, like neurofibromatosis, has been linked with gene mutations. In over 50% of Noonan's cases, a gene called *PTP11* is mutated. When switched on, it directs cells to manufacture a protein called SHP-2 phosphatase. This protein is in a class called protein tyrosine phosphatases, or PTPs, which perform the vital function of removing phosphate groups from molecules. The tweaking of molecules by adding and removing phosphates is an integral part of cell signaling. In Noonan's patients, *PTP11* mutations cause abnormally high activity of SHP-2 phosphatase.

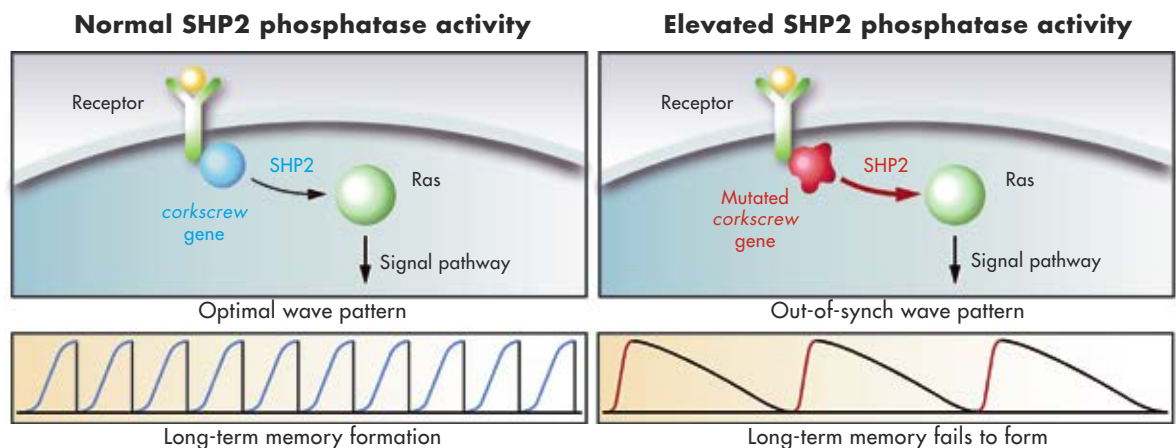
corkscrew is the gene in fruit flies that corresponds with the human gene *PTP11*. Zhong and his team proceeded in their usual fashion: they engineered the human mutation associated with an illness (in this case, Noonan's) into the corresponding fly gene. Then they put the flies through a series of trials that they hoped would reveal new information about precisely how, within neurons, the mutation disrupted normal function, including memory function.

Surprising discovery

“We learned something that really surprised us,” Zhong relates. It was the first of his lab's recent string of memory-related discoveries. They discovered the mechanism of something called the spacing effect, a phenomenon that “had long been known about, but that no one previously understood at the molecular level,” Zhong says. Anyone



In flies, long-term memory forms only after 10 successive peaks and troughs of MAPK activity induced by training sessions; the pattern, and interval between waves (spacing effect) is affected by SHP-2 phosphatase levels.



who has studied for a test has probably experienced the spacing effect. Cramming information into your brain for long uninterrupted stretches is not likely to result in a high mark. We tend to remember what we learn for longer periods when we study at periodic intervals, spaced out between rest intervals.

But why and how? Zhong and his team discovered it is SHP-2 phosphatase that controls the spacing effect, by determining how long the resting intervals need to last so that long-term memories can form. Specifically, they found that under normal conditions (that is, when *corkscrew* is not mutated), as each learning period ends, SHP-2 phosphatase activity inside stimulated neurons triggers a wave of biochemical signals. "And the key," says Zhong, "is that these signals have to peak — rise above a certain threshold — before the next learning session can begin. Repeated formation and decay of the wave — 10 peaks and troughs, in the fly — is needed before a long-term memory can form."

When the *corkscrew* gene in flies is mutated and SHP-2 phosphatase activity is above normal, the "wave" pattern that Zhong describes falls out of synch. Long-term memories fail to form — the analogue of what happens, he postulates, in Noonan's patients who have the *PTP11* mutation. Perhaps most intriguing about this series of experiments is the fact that Zhong's team was able to reverse the memory deficiency in flies, in two ways. When the rest interval between "learning" sessions was increased from 15 to 40 minutes, long-term memories could form, despite the mutation; the same result was also obtained when SHP-2 activity was reduced to normal levels with the help of drugs. It's hypothesized that by increasing the rest period between learning sessions, people with learning disabilities like those that occur in Noonan's might be helped.

In February and March of this year, the team published additional important findings about memory. In one study, Zhong and colleagues at Tsinghua University in Beijing succeeded in specifying a single protein in neurons whose activity mediates three kinds of forgetting. This was big news. "Contrary to the prevailing view, we showed for the first time that the forgetting of short-term memories is an active process in the fly brain, not a passive one," Zhong summarizes. The team showed that by raising and lowering the activity of a protein called Rac (a member of the Rho family of small GTPases, important in cell signaling) they were able to speed and slow short-term memory erasure. By elevating Rac activity, they caused short-term memories to decay faster than normal — a process that worked in the opposite direction, too.

The team's next newsworthy paper, published in March, may be the most exciting of all. It also focused on the action of a single protein — this time, an enzyme called PI3 kinase. Long suspected of playing a protective role against mechanisms at work in the brains of Alzheimer's patients that impair memory, PI3 kinase proved in Zhong's new studies to have the opposite impact. When the team blocked it, they prevented the loss of memory in flies induced by the kind of plaques — toxic clumps of protein fragments — associated with memory loss in Alzheimer's.

"We still don't understand what the 'stuff' of memory is, in spite of the many advances in recent years. But we are getting to the bottom of the question," says Zhong. "The pleasing thought is that memory is just one example of how all information is encoded in the brain. This is work that is going to help with treatments for mental retardation, Alzheimer's and other illnesses associated with memory impairment. But it is also one of the best ways to find out very fundamental things about how the brain works."

Peter Tarr

One experiment

How do tumors progress? A technique devised by a CSHL team led by Drs. Mike Wigler and Jim Hicks might help answer this question and point to tumor-halting strategies.

As tumor cells multiply, pieces of their chromosomal DNA break off, get deleted or copied over and over. A single tumor thus becomes a mosaic of distinct subpopulations of cells with different mutational changes.



Like detectives solving a crime by piecing together a timeline of events, the CSHL team is using their new technique to infer tumor progression by building a timeline of when these various populations appear within the tumor and how they are spatially organized.

The image, by graduate student Nicholas Navin, shows such organization within a section of a ductal carcinoma, a type of breast cancer. Each colored spot within the tumor section corresponds to a cell's nucleus, where DNA is stored. Normal cells (green) that support the tumor's structure coexist with two tumor cell subpopulations (yellow and red) whose larger nuclei contain more DNA. This increased DNA content is due to the repeated copying of a chromosomal region, which creates extra copies of a particular cancer-causing gene.

The new technique, which involves the use of fluorescent tags that stick exclusively to this gene, can distinguish between tumor subpopulations that have two copies of the gene (yellow) and those that have more than ten gene copies (red). Such detailed analysis of a tumor's genetic landscape could be clinically valuable, to design gene-specific therapies that eliminate all subpopulations within a tumor.

Hema Bashyam

Watson School 2010 graduates

In its 11th year, the Watson School has produced a bountiful harvest.

Ten extraordinarily talented students, who all matriculated between 2004 and 2006, earned Ph.D.s this April. Here's a brief glimpse into their work and experiences at CSHL.

Hema Bashyam

Galen Collins

Wabash College
Beckman Graduate Student
"Activator Turnover and Proteolysis in Transcriptional Activation"

In William Tansey's laboratory, Galen worked on the seemingly existential question of how the very first step in a protein's life—its production from genes—is linked to the very last step—its destruction by a cellular machine called the proteasome. Galen's research shows that the proteasome can actually help switch on genes (and trigger protein production) by increasing the turnover of the genes' "on" switches.



Yaniv Erlich

Tel Aviv University
Goldberg-Lindsay Fellow
"Compressed Sequencing"

Yaniv came to CSHL after hearing his college mentor describe it as "the Mecca of molecular biology." In Greg Hannon's laboratory, he worked at the interface of biology and computing, developing, among other things, a novel method that uses the logic of the popular game Sudoku to harness the power of next-generation DNA sequencing. He is the third Watson School student to win the prestigious Weintraub Award, an international prize for outstanding graduate research.



Oliver Fregoso

University of California, Santa Cruz
Seraph Foundation Fellow
William Randolph Hearst Scholar
"Elucidating the Functions of Splicing Regulatory Proteins Through the Use of High-Throughput Proteomics"

In Adrain Krainer's laboratory, Oliver learned "to approach scientific questions critically and creatively." Krainer is a leader in the field of RNA splicing, the process by which RNA transcripts made from DNA are edited before being translated into protein. Oliver applied the tools of proteomics—the large-scale analysis of the structure and function of proteins—to decipher how proteins that modulate splicing also regulate other processes within the cell.



Amy Leung

Cornell University
Beckman Graduate Student
"Regulation of Chromatin by Histone H2B Ubiquitylation"

As a participant in the Undergraduate Research Program (URP) at CSHL, Amy found that the faculty "makes it a priority to teach and mentor young scientists," and stayed for graduate studies. In William Tansey's laboratory, she investigated how genes are turned on and off at the right time even though cells tightly package their DNA into structures called chromatin. She showed how the attachment of a molecule, ubiquitin, to certain chromatin proteins alters chromatin, and thereby, gene activity.



Hiroshi Makino

University of St. Andrews
Elisabeth Sloan Livingston Fellow
"AMPA Receptor Dynamics and Synaptic Plasticity at Excitatory Synapses"

Communication between the brain's neurons is strengthened when molecules called receptors amass at the synapse, the gap between neurons. Mentored by Roberto Malinow, Hiroshi resolved the long-standing controversy of how some of these molecules, the AMPA receptors, are derived and how they help control neural plasticity — a key requirement for learning and memory.



Colin Malone

Washington University, St. Louis
Beckman Graduate Student
NSF Graduate Research Fellow
*"Evolution, Inheritance and
Specialization of Transposon Control
Pathways in Drosophila"*

Colin came to the Watson School knowing that "its Ph.D. program is not for the faint of heart." In Greg Hannon's laboratory, Colin studied the biology of small RNAs, uncovering several features about their role in defending the genome against genetic parasites. He also found that like DNA, small RNAs are vehicles of inheritance, passing on epigenetic information from mother to offspring in fruit flies.



Katherine McJunkin

Princeton University
Robert and Teresa Lindsay Fellow
*"Inducible RNAi Targeting Essential
Genes"*

Katie's doctoral work in Scott Lowe's laboratory has helped expand the applications of RNA interference (RNAi) technology and widened the frontiers of mouse genetics to unravel cancer's genetic basis. With the goal of discovering genes that could be targeted by cancer drugs, she used RNAi to switch genes on or off in a reversible manner in animal models to study their roles in maintaining cancer progression and malignancy.



Shraddha Pai

University of Waterloo
Charles A. Dana Fellow
*"Neuroanatomical Localization of
Timing-Specific Brain Loci in the Rat"*

Motivated by her mentor Carlos Brody's motto that "scientific research requires the attitude of a marathon runner," Shraddha investigated how time and temporal patterns are sensed and represented in the brain. She developed experiments to teach rats to discriminate sound durations and frequencies, and carried out surgery to identify brain spots that mediate the ability to time a cue.



David Simpson

University of California, Davis
Beckman Graduate Student
Department of Defense
Breast Cancer Research Program
Predoctoral Trainee
*"Regulation of Myc-Induced
Apoptosis in Mammary Epithelia"*

When normal breast tissue transforms into invasive cancer, cells lose their organization and fail to suppress cancer-promoting genes. In William Tansey's laboratory, David investigated the role of cancer-causing gene Myc, which is mutated in more than 50% of cancers, in this process. His work, performed in three-dimensional cell cultures that mimic structures in the human breast, provides new insight into how this enigmatic oncogene functions in human cancers.



Oliver Tam

University of Sydney
Bristol-Myers Squibb Fellow
*"Characterization of Small RNA
Populations and DNA Methylation
in Mammalian Development"*

Oliver's thesis, undertaken in Greg Hannon's lab, delved into the role played by families of small RNAs and DNA-modifying methyl groups in epigenetically controlling gene expression. Such epigenetic regulation is what enables multicellular organisms to develop different tissues and organs. In the spirit of his mentor's tendency "to diversify and innovate," Oliver also addressed these biological questions with computational tools that he learned to build.





RESEARCH PROFILE

Adrian Krainer

Tinkering with the cell's RNA-editing process yields payoff in treating a deadly genetic disease

Tucked into a list of several dozen neuromuscular disorders is a killer of a disease called Spinal Muscular Atrophy (SMA). Although not as well known as Lou Gehrig's, Duchenne's, or other muscular dystrophies, SMA is, in fact, the No. 1 genetic cause of death among children under the age of two. At Cold Spring Harbor Laboratory, Adrian Krainer is working steadily to wipe SMA off this list.

Spurring him toward success are his breakthroughs over the last 25 years in deciphering the intricacies of alternative splicing, a cellular process for editing RNA — the chemical cousin of DNA. In the last five years, Krainer has used his insights into this process to correct the splicing defect that causes SMA, in systems of increasing complexity — first in test tubes, then in cells taken from SMA patients and grown in the lab, and most recently, in genetically engineered mouse models of SMA.

"A few more key steps remain before we can petition the Federal Drug Administration for clinical trials," cautions Krainer. Still, his SMA-focused efforts have the potential for a wider payoff. His strategy, honed on the genetics of SMA, could be applicable to other human diseases caused by defective splicing.

An early, cell-free success

When a gene is switched "on" or expressed, its DNA is decoded letter-by-letter into RNA in several steps. The first RNA draft—called pre-messenger RNA (pre-mRNA)—includes chunks of useless information, called introns. So like extra footage cut out of a film, these bits of RNA are lopped off and the remaining bits, called exons, are spliced together to make messenger RNA, which then gets translated into a protein.

Rich Roberts, then at CSHL, and Phil Sharp of MIT — who both later won the Nobel Prize in 1993— discovered RNA splicing in 1977, the year Krainer arrived from his native Uruguay to enroll as an undergraduate at Columbia University. When he began graduate studies at Harvard University four years later, scientists were still unclear about how splicing worked and what molecules were involved.

"It was difficult to get at this question because of problems with reproducing this process in a test tube," recalls Krainer, who soon accomplished this feat. With components extracted from cells that had been split open, he developed an efficient "cell-free" system that is still used by scientists to work out the rules and steps of splicing. Krainer and his colleagues proved the system's usefulness right away by recreating disease-causing splicing defects in the test tube.

Presenting this work at a CSHL meeting in 1984 and at an international meeting in Rome in 1985, he caught the eye of CSHL's Roberts, who was trying to recruit promising young talent. For Krainer, the road from Rome led straight to CSHL. He arrived on campus in 1986 as the first member of the CSH Fellows program, in which newly minted Ph.D.s and M.D.s tackle independent research projects before taking faculty positions.

Switching to alternative splicing

Since that time, Krainer has discovered many of splicing's principles, unraveled how splice-altering mutations can cause disease, and concocted ways to correct faulty splicing. His research group also explores how numerous proteins and RNAs involved in splicing can multitask and regulate a host of other essential processes inside the cell. Krainer was the first, in fact, to discover one of these splicing proteins, in 1989, after a long hunt. For three years, he and a technician grew "liters of cells" and

fractionated their extracts for countless hours in room-sized refrigerators before finding the elusive prize, which now goes by the name SF2/ASF. Today, more than 200 splicing proteins have been found. “Had I known then how complicated the picture of splicing would get, I might not have started down this road,” he jokes ruefully.

The cell’s splicing machinery includes more than just enzymes that cut out introns and paste together exons. SF2/ASF, for example, promotes splicing by acting as a bridge: one end sticks to the pre-mRNA, while the other end tethers protein and RNA components that eventually do the actual cutting and pasting.

While exploring the activity of splicing factors, Krainer, who was appointed full professor in 1994, came to appreciate the power of alternative splicing, which allows a single gene to give rise to multiple versions of a protein. Via this process, a gene’s exons can be mixed in different combinations to generate different messenger RNAs, each carrying the recipe for a different protein.

Krainer’s team found that the choice of which exons to include is guided by splicing proteins like SF2/ASF, which stick to pre-mRNA at specific sites near the exons called “enhancers.” This guiding is dosage-dependent — different protein isoforms are made depending on how much SF2/ASF is available. Working with bioinformatics experts at CSHL, including Michael Zhang’s group,

Krainer’s team has developed computational tools to identify splicing enhancers and their counterparts—called splicing silencers—within exon and intron sequences of large genomes, including that of humans.

A few years ago, Krainer began focusing on splicing defects caused by mutations, many of which had been linked to catastrophic diseases, including a host of neurological disorders. “Such mutations cause exons to be unintentionally included or crucial exons to be erroneously skipped, leading to missing or poorly functioning proteins,” he explains.

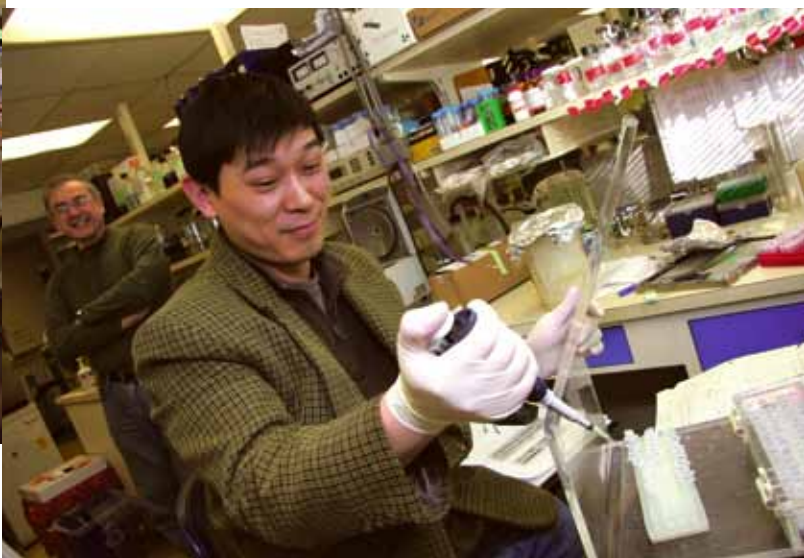
Fixing SMA

A splicing-related neuromuscular disease that grabbed his attention was SMA, which is caused by a deficiency of the SMN (Survival of Motor Neuron) protein. When SMN levels are low in the spinal cord’s motor neurons, they and the muscles they control waste away. Hence babies born with SMA progressively lose the ability to move, swallow, and breathe.

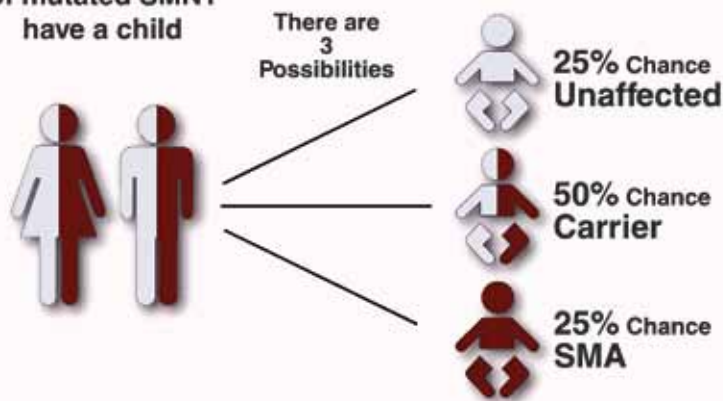
SMN protein is produced by the *SMN1* gene, which is deleted or mutated in SMA patients. Humans have a second gene, *SMN2*, which produces an identical protein. But *SMN2* is a poor backup. It differs from the *SMN1* gene by a single DNA “letter”—a T (thymine) instead of C (cytosine)—near the start of exon 7. This minuscule change causes this exon to often be skipped during splicing, resulting in low levels of full-length SMN protein.



Bench work: Adrian Krainer discusses splicing experiments with postdoctoral researcher Mads Jensen (left photo) and Research Investigator Yimin Hua (right photo)



When two carriers
of mutated SMN1
have a child



1 in 40 People **Unknowingly**
Carry the Gene



Krainer and former postdoc Luca Cartegni found that this skipping occurred at least in part because SF2/ASF failed to attach to the correct enhancer element in the SMN2 pre-mRNA. To correct the error, they created a "designer" molecule – a synthetic chimera in which SF2/ASF's enzyme-binding part was joined to a custom-designed synthetic RNA that can be made to bind any sequence within cellular pre-mRNA by pairing up with its RNA "letters."

So even if a cell's own SF2/ASF performs faultily, its synthetic replacement gets the job done. Krainer's team has proved this strategy's versatility by using it to correct a splicing defect in *BRCA1*, the breast cancer gene. His lab continues to explore the connections between defective splicing and cancer.

The SMA team, led by Research Investigator Yimin Hua, is currently moving forward with another, simpler, synthetic molecule called an anti-sense oligonucleotide (ASO), which works much more efficiently in cells. The ASOs, developed in collaboration with California-based Isis Pharmaceuticals (and Massachusetts-based Genzyme Corporation), can fix SMN2 splicing in test tubes, in patients' cells grown in the lab, and in mice that have been engineered to carry a human SMN2 gene. "The ASO, delivered straight into the fluid that surrounds the brain and spinal cord, protects nerve cells, improves muscle function, and prolongs the animals' lives," explains Krainer.

In a parallel approach with Boston-based Paratek Pharmaceuticals and former postdoc Michelle Hastings, now at Rosalind Franklin University in Chicago, the team has found a molecule that resembles the common antibiotic tetracycline, which also boosts SMN levels in mouse models. This collaboration, initiated by funding from the patient-support group Families of SMA, is now focusing on preclinical drug development.

As Krainer marches on toward translating these successes into viable clinical therapies, he is well aware of the challenges that remain. So are the many parents of SMA-affected kids, who attend his presentations at SMA support group meetings.

"The parents ask some of the most insightful questions about the data that I present," says Krainer. "When we start discussing the nitty-gritty of various splicing mechanisms, I try to convince them to drop what they're doing and come join my research team."

"In some ways, we've moved faster than I thought we could when I first started working on SMA 10 years ago. But in other ways, it never moves fast enough."

Hema Bashyam



Fighting SMA

Krainer is an active participant in organizations like Fight SMA and Families of SMA, and also interacts with the SMA Foundation, and the Muscular Dystrophy Association, all of which have raised funds to support several of his research projects over the years. He often accompanies SMA-affected families to speak with legislators to advocate for the SMA Treatment Acceleration Act, which aims to increase federal funding for SMA research and coordination between clinical centers.

"SMA research is providing valuable insight into so many splicing-related genetic diseases," explains Krainer. Sharing this opinion, the National Institutes of Health chose SMA to be a model for translational research, fast-tracking efforts to bring lab-based discoveries to the clinic.

Faculty & Friends



Damon Runyon-Rachleff Innovation Award

Assistant Professor Raffaella Sordella, Ph.D., received the 2010 Damon Runyon-Rachleff Innovation Award from the Damon Runyon Cancer Research Foundation. The grant of \$450,000 is awarded each year to early-career scientists whose novel approaches have the potential to significantly impact the prevention, diagnosis and treatment of cancer. Sordella is developing new constructs for understanding drug resistance in cancer, particularly lung cancer.

Pancreatic Cancer Research Consortium

The Lustgarten Foundation has established a national consortium involving CSHL and five other institutions to advance research aimed at finding a cure for pancreatic cancer. This year, the Foundation is providing \$10 million for studies on the prevention, diagnosis and treatment of what is now the fourth-leading cause of cancer deaths in the U.S.

The consortium includes CSHL Cancer Center Director Bruce Stillman and Deputy Director Scott Lowe, as well as top investigators from the Dana-Farber Cancer Institute and Harvard Medical

School, The David H. Koch Institute for Integrative Cancer Research at MIT, Johns Hopkins University School of Medicine, Memorial Sloan-Kettering Cancer Center, and the University of Texas M. D. Anderson Cancer Center.

One project based at CSHL will identify targets for new drug therapies based on genetic analysis. The research will combine comprehensive RNAi screening with preclinical studies in mouse models to identify genetic vulnerabilities in pancreatic cancer cells. Other CSHL scientists will study a therapy targeted at the *K-ras* gene pathway. The *K-ras* gene is the most frequently mutated gene in pancreatic cancer.



2010 WSBS Honorary Degree Recipients

At this year's WSBS Commencement Convocation, honorary degrees were conferred upon Carla Jo Shatz, Ph.D., and Thomas R. Cech, Ph.D. Dr. Cech is a Nobel laureate and pioneer in the study of RNA enzymes and telomerase, the enzyme that helps add DNA at chromosome ends. His Nobel prize-winning discovery of self-splicing RNA overturned the conventional wisdom that biological reactions are always catalyzed by proteins. Cech served as the president of the Howard Hughes Medical Institute from 2000-2009 before returning to full-time research and teaching at the University of Colorado – Boulder, where he is a Distinguished Professor and director of the Colorado Initiative in Molecular Biology.

Dr. Shatz is a professor of biology and neurobiology, and director of the Bio-X program at Stanford University School of Medicine. Her research has helped establish some of the basic principles of early brain development. She found that the spontaneous activity of neurons *in utero* is critical for the formation of precise and orderly neural connections in the central nervous system. Her current work focuses on development of the mammalian visual system.

Faculty & Friends

CSHL Ranked #1 Globally in Research Impact

Published research in molecular biology and genetics performed by scientists at Cold Spring Harbor Laboratory has been more influential over the last decade than research performed anywhere else in the world, according to a survey compiled by Thomson Reuters, which is well known for its Essential Science Indicators. It places CSHL atop a list of 20 “heavy hitters” selected from a database comprising over 42,000 institutions worldwide. At its heart, the survey attempts to measure

the impact of research performed at an institution based on how frequently the work produced by its scientists is cited by their peers. It favors influence over sheer number of research papers generated. Over the last decade, papers by CSHL scientists were cited an average of 95 times each, while those of the nearest two peer institutions, MIT and the Salk Institute for Biological Studies, drew an average of 82 and 70 citations, respectively. Per-paper citation figures for Rockefeller, Harvard and Stanford ranged from 62 to 52.



New CSHL Trustees are Elected

At the February meeting of the CSHL Board of Trustees, Chairman Eduardo Mestre presided over the election of two new members: Tania Baker, Ph.D., E.C. Whitehead Professor in MIT's Department of Biology and Howard Hughes Medical Institute Investigator; and Howard Lee Morgan, Ph.D., President of Arca Group Inc. and a Director of Idealab, a Pasadena-based creator and operator of internet companies.

Harold M. Weintraub Graduate Student Award

Yaniv Erlich, a 2010 graduate of the Watson School, won this year's Harold M. Weintraub Graduate Student Award for outstanding achievement during graduate studies in the biological sciences, sponsored by the Basic Sciences Division of the Fred Hutchinson Cancer Research Center. As a student in Professor Greg Hannon's lab, Erlich worked at the interface between biology and computation. He developed a novel method based on the logic of the popular Sudoku puzzle, which harnesses the power of next-generation DNA sequencing to analyze tens of thousands of human DNA samples simultaneously.

Alexander Krasnitz named Assistant Professor, Head of Functional Genomics

Alex Krasnitz was recently promoted to Assistant Professor at CSHL. His research focuses on: the genomics of cancer; machine learning for biology; inference from 'noisy' biological data; and large-scale numerical computing. Notably, Krasnitz has developed a comprehensive method to analyze multiple-genome data sets for breast, lung, colon and liver cancer. It is widely used at CSHL among cancer biologists engaged in studies involving mouse models and RNAi.





75th Cold Spring Harbor Symposium on Quantitative Biology

Nuclear Organization & Function

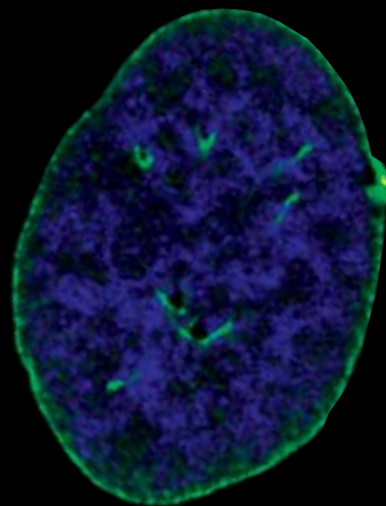
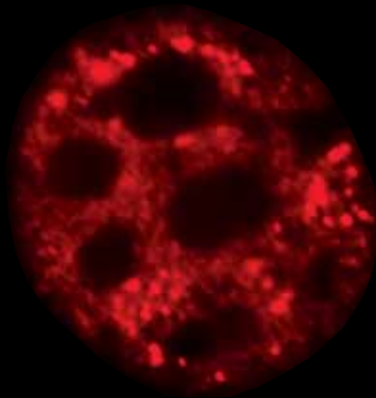
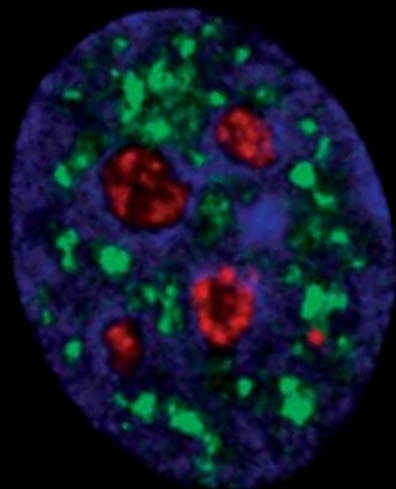
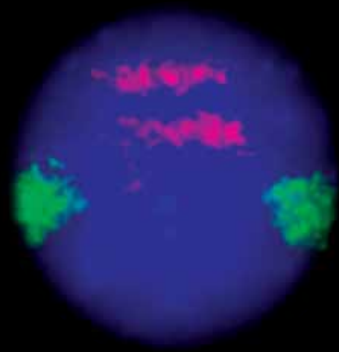
June 2 - 7, 2010

Speakers

Abstracts due March 12, 2010

Organizers:

Terri Grodzicker, David Spector,
David Stewart & Bruce Stillman
Cold Spring Harbor Laboratory



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David Allis, The Rockefeller University
Robin Allshire, Wellcome Trust Centre for Cell Biology, UK
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Richard Young, Whitehead Institute/MIT
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Top left: S. Boyle, MRC Genetics Unit, Edinburgh
Top right: K.V. Prasanth, CSHL
Bottom left: P.A. Babulya, CSHL
Bottom right: R.I. Kumaran, CSHL



Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

Upcoming public lectures @ Grace Auditorium



7:00 PM
8 June **Tue**

Next-Generation Cancer Research:

Long Island Teens on the Front Line of Discovery

7:00 PM
29 June **Tue**

Addiction: How the Brain Measures Reward & Response

3:00 PM
26 Sept **Sun**

Hitting Leukemia Where it Hurts: Researchers and Physicians Unite to Knock Out Cancer

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

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