COLD SPRING HARBOR LABORATORY
Volume 32 • Issue 1 • 2012

HARBOR TRANSCRIPT

Spinning Off Success

From lab bench to market

PRESIDENT'S MESSAGE

In the sciences, the publication of a research discovery is a measure of success. Publish or perish, as the saying goes. A global network of scientific journals like our own *Genes & Development* and *Genome Research*, which you'll read more about here, has developed as a means to communicate the latest developments. Both where and how often a scientist publishes research results are metrics of success, but not the only measure.

CSHL is consistently ranked by Thomson Reuters as No. 1 in the world for the impact of our research in molecular biology and genetics. That we are No. 1 means that research papers by CSHL scientists are cited more frequently than the papers of investigators at leading peer institutions, but we should be careful of resting on our laurels. Barbara McClintock would not have had a high impact factor when she performed her major, Nobel Prize winning research because she was far ahead of her time.

In this *Harbor Transcript*, we offer several other distinctly different perspectives on how to measure our impact. Over the past few decades, CSHL has been a breeding ground for biotechnology and many of our biggest scientific breakthroughs have sewn the seeds for biotech companies. CSHL has spun off over 20 companies and there are more to come. This is one very concrete way of measuring the impact of our science, yet it does not tell the whole story by any means for it only indirectly reflects the very basic, curiosity driven research that we are famous for. Our future will still be driven by fundamental, discovery science.

At the Watson School of Biological Sciences, our graduates are another measure of our success, particularly in basic, fundamental science. In just a short 10 years, WSBS students have been authors on over 185 research papers and 11 of our graduates have secured tenure-track faculty positions at major research institutions. On pages 13–14, you can learn about our five newest graduates — what drew them to the Watson School, what they worked on while they were here, and where they plan to take the next step in their blossoming careers. I look to this next generation of Ph.D.s that CSHL has trained to continue to make us shine.

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Courtesy Mirimus: 4;
Courtesy Mike Wigler: 5;
Courtesy Nick Tonks: 11;
Constance Burkin: 13–14;
Chris Gazzo: 15;
Courtesy David Peikon: 16;
Courtesy Catherine Dougherty: 17

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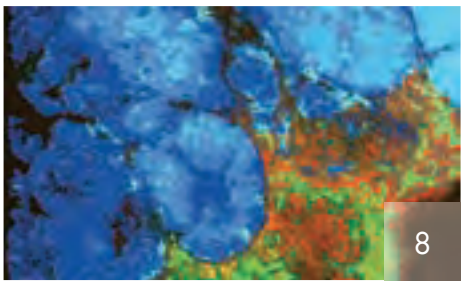
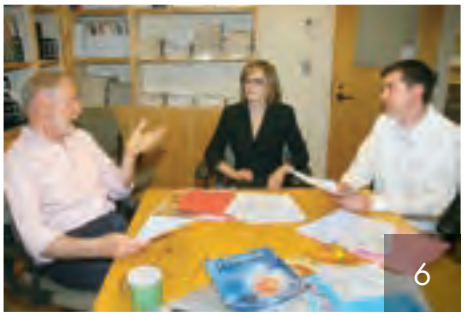
Volume 32 • Issue 1 • 2012

Grad student Fauzia Chaudhary (foreground) and Postdoc Navasona Krishnan under watchful eye of mentor Professor Nick Tonks





FEATURES

FACULTY & FRIENDS

On the cover:
Having co-developed a high-throughput, automated microscopy platform called Serial Two-photon (STP) Tomography for imaging whole mouse brains, CSHL Associate Professor Pavel Osten has launched a spin-off company that is applying this technology to drug discovery in neuroscience.

Spinning off success

Bringing basic research from lab bench to market

John Maroney (seated, right) discusses a new technology transfer opportunity with colleagues Jason Wen and Vlad Drozdoff (standing).

Scientists at Cold Spring Harbor Laboratory have a long history of producing groundbreaking discoveries and technological innovations that have revolutionized entire fields of science. Most of this research appears within highly cited publications. Some of it has captured public acclaim and high honors, including eight Nobel Prizes. And some of it has also served as the springboard for commercial ventures that have turned fundamental discoveries into products, jobs and most importantly, advances in human health.

Since the 1980s, research done at CSHL has been, in part or in whole, the founding basis of many biotechnology startup companies. The "technology transfer" income from these, along with technology licensing activity and corporate partnerships, is an important source of support for the always productive basic science research engine at CSHL.

Regional economic development studies often tout the following as the key ingredients that academic institutions need to achieve startup success: large departments in engineering, math and other physical sciences; and geographical proximity to and symbiotic existence with hi-tech industrial hubs. CSHL has found its strength in other virtues.

"What we do have is an influx of scientific talent from all over the world, which has made CSHL rich in intellectual capital," says John Maroney, Vice President and Director of CSHL's Office of Technology Transfer, which has helped CSHL-related startups to take root all over the nation. "The ability of CSHL scientists to create technology that is highly regarded by the world's research community and also valued by the biomedical industry has helped launch commercial endeavors."

The Laboratory's efforts in technology transfer began in the 1980s with the growing realization that others were reaping the financial benefits of CSHL technology without providing any of the support needed to create and develop those technologies. For example, a company that commercialized enzyme purification technology developed in the 1970s by then CSHL scientist and Nobelist Rich Roberts had grown into the hugely successful Massachusetts-based New England Biolabs. But none of the revenue benefitted the CSHL research programs that had led to the company's commercial success.

That's when Maroney, with the support of the Laboratory's leadership and scientists began to establish agreements with commercial organizations that would complement both basic academic research at CSHL as well as the commercial application of its results for public good. CSHL scientists have kept him and his team busy ever since in securing intellectual property rights, developing patents, licensing technologies and launching startups [see timeline].

As it gained experience in tech transfer, the Laboratory achieved several early successes, including the launch of Oncogene Science in 1983. Inspired by the discovery of the first human cancer gene, the oncogene *Ras*, by CSHL scientist Mike Wigler, OSI Pharmaceuticals, as it eventually became known, became a huge success. Responsible for creating hundreds of high paying jobs on Long Island, it gained fame internationally after it developed the drug Tarceva® to treat lung, pancreatic and other types of cancer. A genetic screening platform developed by Wigler helped launch another startup in 1983 called Icos Corp., which used this technology to identify the enzyme inhibitor that would gain worldwide fame as the drug Cialis®.

In the following decade, a stream of innovations from Wigler's group rapidly lengthened the lineup of CSHL's spin-offs: a gene co-amplification method that helped produce vast quantities of blood clotting factors and other biological products; a technique to accelerate the design, testing and analysis of small synthetic peptides for use as inhibitors of biomolecules (Pharmacopeia, Inc.); and a method called Representational Difference Analysis (RDA) to identify oncogenes and tumor suppressor genes by comparing cancer cell DNA to a normal cell's DNA. This last technology was the founding basis of Amplicon Corp., a startup that was acquired by Tularik Inc. (which was later purchased by biotech giant Amgen). "That's how Mike and CSHL contributed to the creation of the biotech industry," says Maroney.

CSHL had emerged as a genome sequencing powerhouse in the late '90s and early 2000s as a result of its key role in international collaborations that sequenced various species, including humans. In a bid to sequence

Startups based on CSHL innovations

1981 Protein Databases Inc.
Based on software developed by Jim Garrells to analyze patterns in 2-dimensional gel electrophoresis arrays of cellular proteins; acquired by Bio-Rad Laboratories.

1983 Oncogene Science (OSI) Initiated after breakthrough discovery of *Ras* oncogene by Mike Wigler; developed cancer drug Tarceva®.

1990 ICOS Corp.
Highly successful spin-off that developed the blockbuster drug Cialis® based on gene cloning technology patented by Mike Wigler.

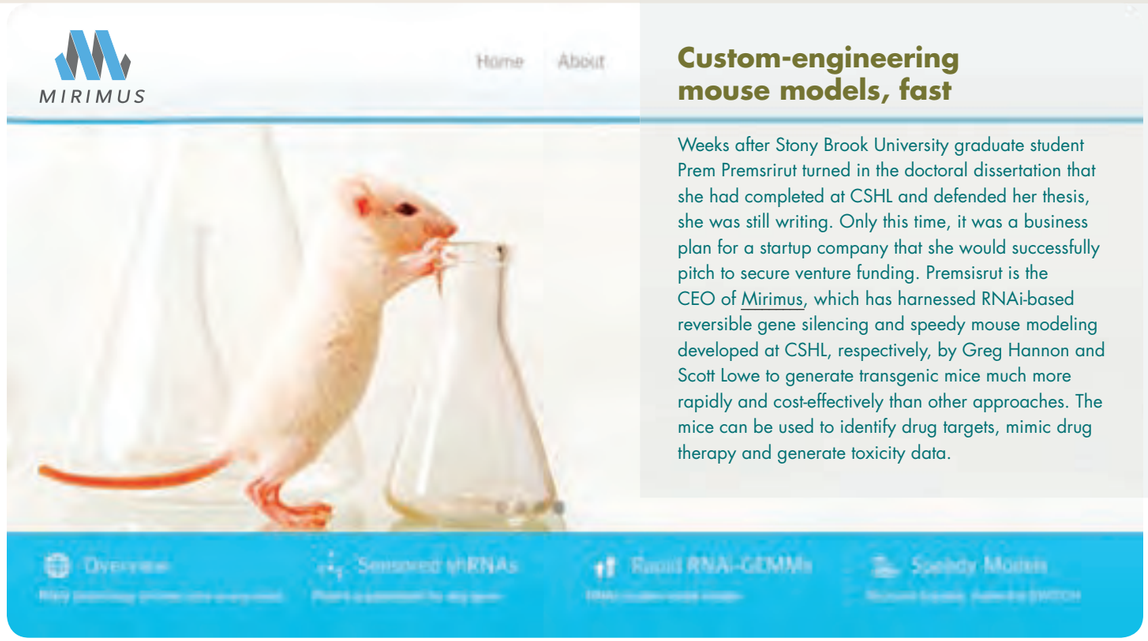
1991 Pathogenesis Corp.
Infectious disease drug development using Mike Wigler's representational difference analysis (RDA) technology; acquired by Chiron Corp.

1992 Geron Corp.
Partly based on Nobelist Carol Greider's breakthrough research on telomerase; develops cancer- and geriatrics-related therapies.

1992 Mitotix, Inc.
Developed cancer diagnostics and therapies based on David Beach's work on cyclins — proteins involved in the cell cycle; bought by German company GPC Biotech.

1993 Pharmacopeia, Inc.
Based on a successful collaboration between Mike Wigler and scientists at Columbia University in encoded combinatorial libraries for high-throughput drug screening.

1994 Amplicon Corp.
Licensed Mike Wigler's RDA technology to look for genes associated with cancer and other diseases before being acquired by Tularik Inc.



Custom-engineering mouse models, fast

Weeks after Stony Brook University graduate student Prem Premsrirut turned in the doctoral dissertation that she had completed at CSHL and defended her thesis, she was still writing. Only this time, it was a business plan for a startup company that she would successfully pitch to secure venture funding. Premsisrut is the CEO of Mirimus, which has harnessed RNAi-based reversible gene silencing and speedy mouse modeling developed at CSHL, respectively, by Greg Hannon and Scott Lowe to generate transgenic mice much more rapidly and cost-effectively than other approaches. The mice can be used to identify drug targets, mimic drug therapy and generate toxicity data.

the large genomes of crops like rice and corn, Rob Martienssen and W. Richard McCombie developed a technique called methylation filtration to capture and sequence only the gene-rich regions in the genome. This became the basis of a startup called Orion Genomics, LLC., one of the first companies in a niche that has since become one of the hottest growth sectors within the biotech industry.

The Laboratory's other technological *tour de force* in recent years has been the development of RNA-based tools to silence gene expression by Gregory Hannon, a pioneer in the field of RNA interference (RNAi). The RNAi libraries, as these tools are known, are key to investigating the functions of individual genes and developing new therapies to target those genes that cause disease when they malfunction. In addition to being available to all basic science researchers, Hannon's creations, which have received several patents, have provided the foundations of several commercial ventures, including the recently launched startup, Mirimus, which generates customized mouse models that serve as superior preclinical test subjects in the drug discovery process [see "Custom-engineering mouse models, fast"].

"The system that is in place at the Laboratory to commercialize discovery makes it very easy for people like me," says neuroscientist and Associate Professor Pavel Osten, who won venture capital funding last year to launch Certerra Inc., a startup that also aims to make an important contribution to improving drug discovery. "I'm walking down a well-trodden path."

The company is based on a groundbreaking technology developed by Osten and collaborators at TissueVision Inc. and MIT called Serial Two-photon Tomography. It involves a novel high-throughput microscopy platform that produces speedy, automated image maps of a whole brain at cell-level resolution. Osten's goal is to use this technology to investigate brain circuits in mouse models of brain disorders and map drug-activated brain circuits for preclinical screening of new drugs for the pharmaceutical industry.

Drug companies currently spend up to $1 billion to find out whether a drug compound that worked well in animal testing also works well in human clinical trials. However, the probability of success — the chance that a drug will eventually make it into the market — is low; for drugs targeting the brain, it is a dismal 5%. Osten's approach could help improve the ability of drug developers to predict the outcome of clinical trials before embarking on this long and expensive process [See "'Pharmacomapping' the brain"].

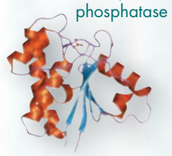
"As we learn more about how neuronal activity patterns change in our mouse models of disorders such as autism and bipolar disorder, and build up a drug-specific pharmacomap database at Certerra Inc., we may eventually be able to make predictions about which drug would be a good bet to reverse the changes that we see in the disease models," says Osten. With most pharma companies cutting their neuroscience and other research programs and lacking fresh ideas for a better drug screening process, Osten's approach, which grew out of a need for better brain visualization techniques, as well as Mirimus's strategy, offer new hope for developing effective drugs faster through a more economically viable pipeline.

'Pharmacomapping' the brain

Here's one scenario of how Certerra's technology might help reduce the failure rate of drugs in clinical trials: Because a drug's effects in the brain are largely determined by which neurons it activates, treating a mouse with an existing drug, say for depression, and mapping subsequent brain activity will generate a 'pharmacomap' for the drug. Simply comparing this map to that generated by new candidate drugs for depression will help pharma companies sift out the duds and focus only on those compounds that work on par or better than the existing benchmark.

At a time when more than 12 million Americans are out of work, investing in basic research might at times provoke a reaction along the lines of "What's in it for me?" The answer is that basic research breakthroughs have defined and driven whole new industries in the last 50 years. Imagine a world without the internet or the semiconductor, robotics and the biotech industries, all sparked by innovations in academic labs.

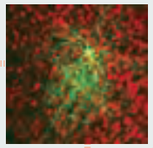
Surveys by The Association of University Technology Managers show that academia-spawned companies continue to crop up at a brisk pace, with 651 created in 2010 alone, up 15% since 2007, emphasizing the potential that academic startups have to continue expanding the job market while introducing innovative and transformative new technologies. It's entirely conceivable that sprouting today within one of CSHL's 50 labs is a scientific or technological breakthrough that will seed the next high-growth company and many new high-paying jobs. **Hema Bashyam**



1995 Charybdis Corp.
Formed to develop and commercialize new classes of small-molecule pharmaceuticals in type 2 diabetes, obesity and oncology, based on protein tyrosine phosphatase discoveries by Nick Tonks.

1996 Genomica Corp.
Licensed a genome scanning technology developed by Tom Marr for genomics-based drug discovery; acquired by Exelixis, Inc.

1997 deVGen
Belgian company based in part on Michael Hentgartner's discoveries of novel cell death-regulating proteins in worms.

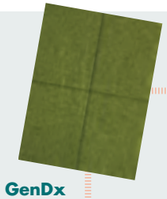


1997 Helicon Therapeutics
Launched by Tim Tully to develop drugs for Alzheimer's, age- and trauma-related memory impairment.

1998 Genetica
Started by David Beach and Gregory Hannon to apply their research on RNAi in the development of high-throughput tools for drug target validation and their work on retrovirus vectors for antibody production.

1998 Orion Genomics, LLC.
Used filtered shotgun sequencing technique invented by Rob Martienssen and Dick McCombie to sequence and analyze plant genomes; now developing diagnostics for multiple cancer types.

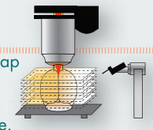
2002 Juventis, Inc.
Based on Grigori Enikolopov's discovery of the role of nitric oxide in controlling the regeneration of stem cells in the brain.



2007 GenDx
Based on Mike Wigler's ROMA (representational oligonucleotide microarray analysis) technology to develop DNA diagnostics for breast cancer.

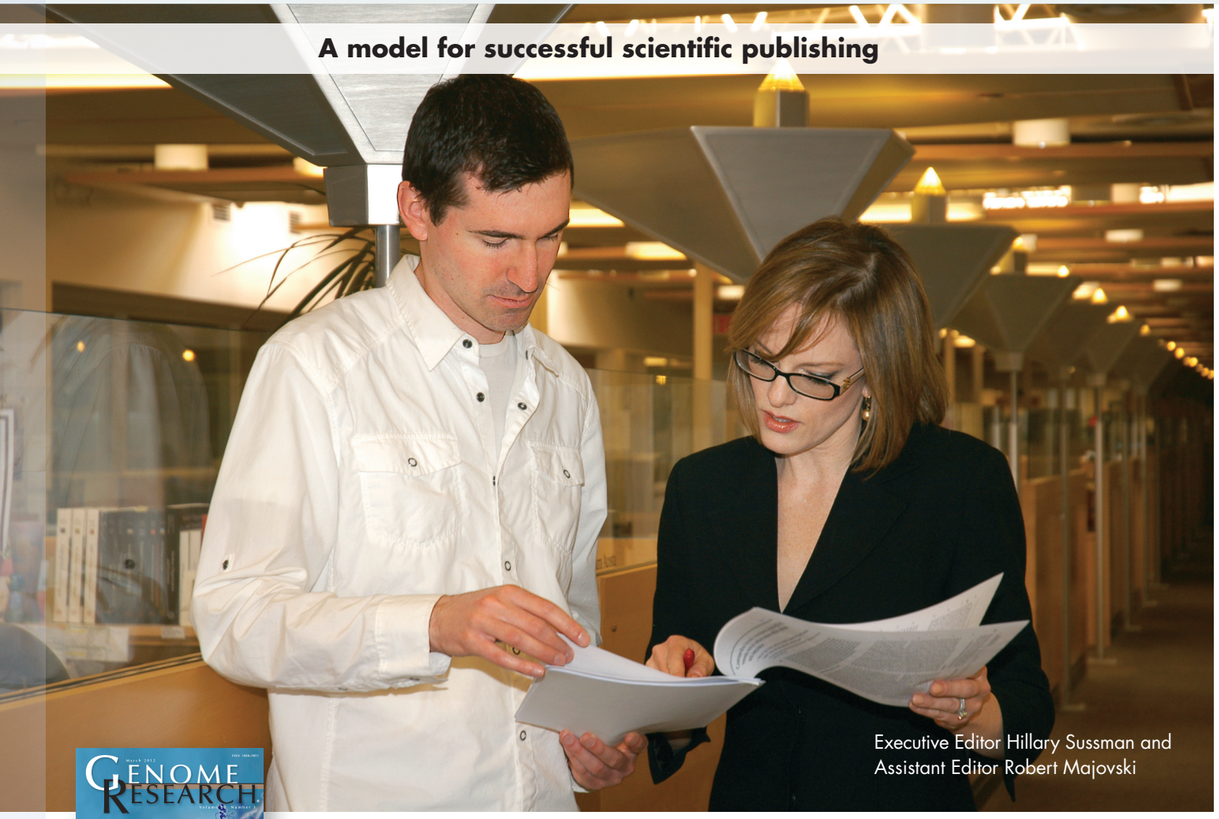
2011 Mirimus
Rapidly customizes mouse models for drug development based on advances in RNAi and mouse modeling by Gregory Hannon and Scott Lowe.

2011 Certerra Inc.
Based on novel platform co-developed by Pavel Osten to quantitatively map drug activity in mouse brains and improve drug discovery in neuroscience.



Genome Research

A model for successful scientific publishing



Executive Editor Hillary Sussman and Assistant Editor Robert Majovski

More than 8000 scientific journals are published each year, some more important and prestigious than others as determined by a metric of worth called the impact factor. The impact factor rankings are released annually by the news and business intelligence company, Thomson Reuters. In the latest report, ranked within the top 1.2 percent are two journals published right here at Cold Spring Harbor Laboratory by the CSHL Press — *Genome Research*, and its slightly older sibling, *Genes & Development* (see sidebar). The report's sub-lists hold more honors for *Genome Research*: it ranks second among journals in the "Genetics and Heredity" and "Biotechnology and Applied Microbiology" categories.

"We're proud that *Genome Research* has become so highly valued by the genomics community," beams Hillary Sussman, who became executive editor of *Genome Research* in 2004 and has steered the journal through a period of increasing prominence. But *GR*, as it's fondly known, has had a great couple of decades right from its launch in August 1991 as a quarterly with the rather unwieldy name of *PCR: Methods and Applications*.

PCR, or polymerase chain reaction, one of the most widely used techniques in science and medicine today, was then one of the hottest areas in biotechnology R&D. "It was a new technology that was not easy to do and it was changing very rapidly," recalls John Inglis, the journal's co-founder and publisher, and executive director of CSHL Press.

Inglis, a proponent of "agile" publishing — a mix of faster, versatile, market-driven publishing strategies — saw a niche for a publication about laboratory techniques, which, unlike a technical manual, would come out regularly but less frequently than a typical journal. He and editor Judy Cuddihy carefully midwifed their new product, negotiating advertising support and inviting an A-list of scientific experts to serve on the editorial board. PCR inventor and Nobelist Kary Mullis signed on; so did luminaries such as Eric Lander, Svante Pääbo, David Botstein and others.

"To succeed, a journal needs great content, a strong editorial board, good advertising backing and a solid subscription base," says Cuddihy. "We had all these things going for us right from the very beginning." The journal was an immediate success. A 1992 review in the journal *Nature* raved, "…if PCR is a religion, *PCR: Methods and Applications* is its Bible."

The journal was an immediate financial success as well, an achievement that other journals can rarely claim. "Most typically break even after five years and recoup their investment by year 10," explains Inglis. "We were profitable by the end of the first year."

In 1995, with PCR innovation beginning to wane and the Human Genome Project well underway, it was clear that a revolution was on its way in the field of genomics. Inglis's team readied for a transition that would sustain their journal's cachet and enhance its value to a research community that was itself in flux.

"Our approach was to parallel the interests of the genomics community, which was then focused on genome sequencing methodologies and bioinformatics," explains Inglis. "But knowing that the community's ultimate aim was to apply genomic analysis to solve biological problems in the lab or even in the clinic, we wanted to have a journal that was also embedded with the seeds to grow into this research area in the future."

With encouragement from then CSHL Director Jim Watson, the team launched the journal's new avatar in August 1995, calling it *Genome Research*. 16 years later, Inglis and Sussman are gratified to see *GR* make the predicted move — from pure methodology to developing new applications for genomics. The scientific editorial board, which remains vital to the journal's success, still includes Eric Green, Rick Myers, and Richard Gibbs from the PCR era, but has expanded to include Aravinda Chakravarti, Bill Pavan, and Evan Eichler. The journal's scope is ever widening. It includes emerging and cross-disciplinary topics such as molecular evolution and neurogenomics in addition to staples such as systems biology and genome structure and function.

"*GR* is also more selective than ever," says Sussman, "with around 15% of all submitted manuscripts being accepted for publication." The rigorous peer review — the thorough vetting process in which a panel of experts debates the merits of each manuscript and the legitimacy of its science — has ensured that only cutting-edge and top-notch papers appear in each issue.

"In a field as diverse and fast-moving as genomics it can be challenging to differentiate the solid science from flashy, technically weak publications," says Daniel MacArthur, a genomics expert at Harvard/MGH who also writes a popular blog for *Wired* magazine. "But if I see something pop up in *GR*'s table of contents, I know it's worth paying close attention to it."

If a strong impact factor is one indication of *GR*'s importance, the frequent coverage of its papers in the mainstream media is another. One recent paper was even featured as one of the top 10 medical breakthroughs of 2011 by *TIME* magazine.

The announcement of the completion of the first draft of the human genome at CSHL's Grace Auditorium more than a decade ago included a promise about the enormous benefits that these results would one day offer to mankind. "We are driven by the goal of helping to deliver this goal and making *GR* the journal that shows genomics matters to human health," says Inglis.

Hema Bashyam

Genes & Development, the oldest among the seven journals published by CSHL Press, celebrates its 25th anniversary this year. The youngest, *CSH Perspectives in Medicine*, launched in September 2011, offers reviews of different aspects of various diseases from AIDS to Alzheimer's that are commissioned by an eminent board of scientists and physicians.

One experiment

Studying cancer in its natural environment — at tumor sites in living animals — provides insights scientists can't obtain when they look at cancer cells isolated in culture dishes. CSHL's Mikala Egeblad and her team have been making time-lapse images of mouse mammary tumors *in vivo*, to learn how tumor cells interact with the tissue in which they are embedded, called stroma.

This image is one frame from a movie made by Egeblad's team — one experiment in a series showing what happens when an anti-cancer drug is injected into a mouse with a breast tumor. The tumor's (blue) lobe-like structure is fed by blood vessels that run between the lobes, invisible here. Spectacularly visible is the fluorescently dyed orange reagent that represents the drug in this experiment. It has leaked from the vessels into stromal space. In the stroma, too, one sees green blotches, cells of the mouse's innate immune system. Mostly macrophages, these cells are responding to the tumor as if it were a wound, bringing growth factors and other agents to help with tissue repair — which in this case only tends to fuel tumor growth. "We're showing one reason why treating cancer is so tricky," explains Egeblad. "The tumor and its environment are in constant flux. We're testing approaches to treat with this in mind, trying to get more drug into the tumor and learning how the innate immune system at different disease stages hinders and helps tumor-fighting, with the goal of getting existing drugs to work better."

Peter Tarr

RESEARCH PROFILE

Nicholas Tonks

Persistence comes naturally to Nick Tonks, FRS, who has the distinction of having laid the foundations for the identification and functional characterization of a "superfamily" of 107 regulatory enzymes called protein tyrosine phosphatases, or PTPs. The experiment that led to his first breakthrough on PTPs was performed in the late 1980s, while he was working with Dr. Edmond Fischer, a revered mentor and future Nobel laureate, who predicted that his approach "will never work."

"Right," Tonks acknowledges today with a hearty laugh. "So I stuck to my guns and got on with the project!" He had already learned that one had to fight for the ideas one believed in, a lesson that has served him repeatedly. Right now, his CSHL lab is honing novel biochemical methods that could form the basis for new classes of therapeutics in diabetes and cancer.

PTP1B: more than a 'housekeeper'

It was Dr. Fischer — Tonks' postdoctoral advisor at the University of Washington, Seattle — who, with co-Nobelist Edwin Krebs, provided the first demonstration of the regulation of a protein by phosphorylation, in the early 1950s.

Protein phosphorylation, which occurs at thousands of sites in most cells, acts like a switch to regulate proteins involved in essential biochemical processes. It is facilitated by a large class of enzymes called **protein kinases**, which transfer a phosphate group from the donor molecule ATP to an amino acid residue — usually a serine or threonine, and less often a tyrosine — on the protein being acted upon, called the substrate. The process, importantly, is reversible; a class of enzymes called **protein phosphatases** recognizes phosphorylated residues and functions to remove the phosphates that kinases have added. It is the under-appreciated protein phosphatases that have been the focus of Tonks' research career, since his days as an undergraduate.

While working with "Eddy" Fischer, Tonks focused on PTPs, phosphatases that specialize in removing phosphates from tyrosine residues. Why tyrosine? Phosphorylation has different implications depending on the identity of the amino acid that is phosphorylated. Tyrosine phosphorylation has been implicated in growth and metabolic regulation and its disruption leads to major diseases such as cancer and diabetes. The cellular receptor for insulin, for example, was known to be a tyrosine kinase that became phosphorylated and activated when insulin bound to it. A PTP, then, would halt the insulin signal in a cell, by removing the critical phosphates that had activated the signal in the first place.

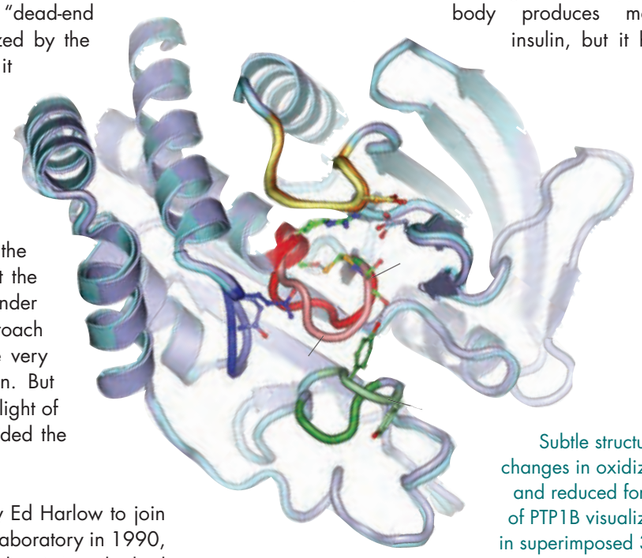
At the start of his career Tonks sought to purify a PTP, something that had not been done before. Then he could sequence it and try to understand its mechanism of action, how it was regulated, and its function. The key step was developing a "dead-end substrate" that would be recognized by the PTP and trapped by it, so that it could be used to extract the PTP from the complex mixture of proteins in a tissue sample. Tonks had discovered how to produce such substrates while doing undergraduate research at Oxford under Sir Philip Randle, and honed the technique as a doctoral student at the University of Dundee in Scotland under Sir Philip Cohen. It was this approach that Dr. Fischer thought would be very challenging, hence his admonition. But Tonks made it work, and, to the delight of all, it led to two papers that provided the foundation for the PTP field.

By the time Tonks was recruited by Ed Harlow to join the faculty at Cold Spring Harbor Laboratory in 1990, there was already evidence that the PTP Tonks had purified, which he named PTP1B, was more than a "housekeeper" for tyrosine kinases, "cleaning up their mess," as Tonks characterizes the then-prevailing wisdom about the entire class of phosphatases. In fact, he and Dr. Fischer had demonstrated the existence of transmembrane "receptor PTPs," which, like receptor kinases, could themselves bind to ligands and directly control the response of cells to environmental stimuli.

The search for a PTP1B inhibitor

In 1999 a team from McGill University generated a line of mice lacking the gene that encodes the PTP1B enzyme. The animals appeared normal, except "they could be fed a high-fat diet, the equivalent of hamburgers and french fries, and they did not get fat," Tonks says. When his team separately showed how PTP1B "recognizes the insulin receptor as a substrate," it became possible to think of a diabetes drug based on inhibition of PTP1B.

"Diabetes is preceded by a resistance to insulin," Tonks explains. Normally, the hormone binds to its receptor — a tyrosine kinase — initiating signaling that directs cells to absorb glucose from the blood and to store it, lowering blood sugar levels. In type 2 diabetes, insulin binds to the receptor but fails to signal properly. The body produces more insulin, but it has



Subtle structural changes in oxidized and reduced forms of PTP1B visualized in superimposed 3-D ribbon diagrams.

no effect. The problem is not a lack of insulin, but a failure of its signal.

PTP1B's role in insulin signaling is normally to antagonize it, via dephosphorylation of the receptor. But, "if you can *suppress* the activity of PTP1B in an insulin-resistant state, you can *facilitate* insulin signaling," Tonks suggests. Based on this concept, he and others — including chemists at major pharmaceutical firms — spent years trying to come up with small-molecule inhibitors of PTP1B. They succeeded; but there were technical problems with delivery of the molecules, deemed insuperable. Big Pharma dropped the idea.

Tonks with postdoctoral researcher Li Li. "I like people who bring their own ideas and passions to the work we do," he says.

True to form, Tonks was not ready to quit. He and colleagues have continued to work on the problem, seeking other solutions. "I firmly believe that the function of academia in these situations is to think outside the box and discover and validate new approaches that we can then present to partners in industry for development into therapeutics," he says.

Several concurrent projects in Tonks' lab show great promise. With postdoc Navasona Krishnan, Tonks has "defined an entirely new mechanism for the inhibition of PTP1B." They are working with an inhibitor that binds to an alternative, allosteric site. This molecule, a natural product, is currently in preclinical testing, and is one of two approaches to diabetes now being pursued. [For the other, see: "Harnessing oxidation"]

Potentially, inhibitors of PTP1B have another important application, in HER2-positive cancers, such as breast cancer. The HER2 oncoprotein — the target for the drug Herceptin — is a tyrosine kinase. Published experiments have shown that mice engineered to express HER2 but to lack the PTP1B gene have "attenuated tumorigenesis and the tumors don't metastasize." This intriguing result suggests that PTP1B plays a *positive* role in transmitting the signal from HER2 and "that if you inhibit PTP1B you could have a new strategy for treating cancers that express HER2," Tonks says. He and Associate Professor Senthil Muthuswamy are currently testing natural-product inhibitors in Muthuswamy's mammary epithelial cell models of breast cancer. Discussions are under way to take this strategy into the clinic in 2012.

"I've been trying to do this kind of thing since the mid-1990s," Tonks says. "And now, for the first time, we have the possibility of getting an inhibitor of that enzyme I purified 25 years ago to treat major human disease. The idea that one's research can lead to treatments for real patients — well, there is no other way to put it. It's just a huge motivating factor." **Peter Tarr**

Harnessing oxidation: an alternative diabetes strategy

Tonks and colleagues have also been working to harness new knowledge they've obtained about how oxidation changes the structure of PTP1B. In excess, oxidation damages living tissue. But controlled production of limited quantities of oxidizing compounds such as hydrogen sulfide, in defined subcellular locations, "makes possible an exquisite level of regulation we didn't know about before," says Tonks. This is true in insulin signaling, where oxidation of PTP1B removes the inhibitory effects of the PTP and enables the signal to be transmitted effectively. Stony Brook University grad student Aftabul Haque last year generated antibodies that selectively recognized the oxidized, inactive form of PTP1B, stabilization of which resulted in enhanced and prolonged insulin signaling in cells. The lab now seeks a small molecule drug that can produce the same effect.

Watson School 2012 graduates


1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1 Patrick Finigan
2 Kyle Honegger
3 Elizabeth Nakasone

Patrick Finigan

Beckman Graduate Student; Anderson Fellow
The origin of novel phenotypic variation in Arabidopsis *allopolyploids*

It may only be a coincidence that Patrick Finigan, having grown up in California's fabled Napa Valley, would be drawn to the work of plant geneticist Rob Martienssen when planning his doctoral research. It was under Martienssen's influence that Finigan focused on experimenting with plants possessing twice their normal genomic content. When hybridized with other plants, these plants proved capable of generating novel properties such as larger fruits. Finigan particularly appreciated his mentor's help in "piecing together disparate bits of science to form a great hypothesis or idea." After graduation, Finnigan says he hopes to pursue a career in the biotechnology industry.


3

Kyle Honegger

Crick-Clay Fellow; NIH Predoctoral Trainee
Neural coding in the Drosophila *mushroom body*

Kyle Honegger came to CSHL from Chicago knowing that he wanted to learn more about imaging brain function *in vivo*. His thesis placed him in the thick of research that Glenn Turner's lab recently published on how neurons in a part of the fly brain called the mushroom body (MB) process and make sense of incoming olfactory signals. This work provided Honegger with an opportunity to help set up new imaging equipment, and to participate in studies which demonstrated the "sparseness" of the neuronal response – the fact that only a few among the total complement of MB neurons are involved in responding to a given odor. Honegger, who says his only difficulty has been in persuading family members back home that "flies actually *do* have brains," now seeks a postdoc position, hoping to study how selective pressures have influenced the evolution of olfactory systems.

Elizabeth Nakasone

Quick Fellow; Hearst Foundation Scholar; U.S. Army Breast Cancer Research Program Predoctoral Fellow
A stromal CCL2/CCR2 signaling axis regulates chemotherapeutic response in a mouse model of breast cancer

Impressed by a research seminar offered by a visting lecturer, Mikala Egeblad, on the importance of the tumor microenvironment in cancer,

Watson School 2012 graduates

4

5

4 Frederick Rollins
5 Zhenxun Wang

Liz Nakasone made arrangements to study with Egeblad once she joined the CSHL faculty in 2009. "Mikala was doing a lot of translational work, and that is what I want to do." Nakasone's dissertation research concerns myeloid cell recruitment to the tumor site following chemotherapy. She focuses on how this aspect of the innate immune response influences the response to chemotherapy and the likelihood of relapse. Grateful for the support she has received from her mentor, who she describes as being "close to the experiments," Nakasone now hopes to continue research on the tumor microenvironment in an academic setting.

Frederick Rollins

Cashin Fellow
The genetics and epigenetics of erlotinib resistance in non-small cell lung cancer

During his time at the Watson School Fred Rollins was involved in research on some of the hottest fields in molecular biology: methods of delivering RNA interference (RNAi) to cells in a therapeutic context; improving cancer screening; and defining the so-called cancer methylome. The latter provided a framework for his thesis research, in the laboratory of Professor and HHMI Investigator Greg Hannon. The methylome in the specific context of cancer is the genome-wide distribution of methylated sequences, which impact gene regulation and expression. Rollins' research focused on how methylation profiles were retained in primary tumors and in various cell lines. Rollins has high praise for his mentor. "Greg is so smart that half the time you walk out of a conversation and say, 'What? Am I supposed to know all these things already?!' He's extremely creative and always seems to ask the right question at the right time." Rollins now contemplates a postdoc job and hopes at some point to be part of a startup that works on the problem of delivering RNAi therapeutics.

Zhenxun Wang

A*STAR National Science Scholar, Singapore
The mechanism and manipulation of PK-M alternative splicing

A native of Singapore, Wang came to the US because he wanted to study molecular biology. And, he says, on the eve of obtaining his doctorate, "I'm in it for keeps." He gravitated to the laboratory of Adrian Krainer, with whom he has performed research on RNA splicing. Specifically, Wang has studied how alternative splicing yields two isoforms of a protein called pyruvate kinase, one of which — PK-M2 — alters cells' ability to metabolize glucose, in a phenomenon known as the Warburg effect which plays an important role in cancer's abnormal metabolism. Wang will now return to Singapore, where he will take up a postdoc at the Agency for Science, Technology and Research (A*STAR). He expects to conduct research in a lab that has recently discovered a new target in cancer metabolism. "What I like about science is solving problems," he says. "Things always go wrong; but in the process of overcoming these difficulties, sometimes you find things that are new. That is pretty rewarding."

Faculty & Friends

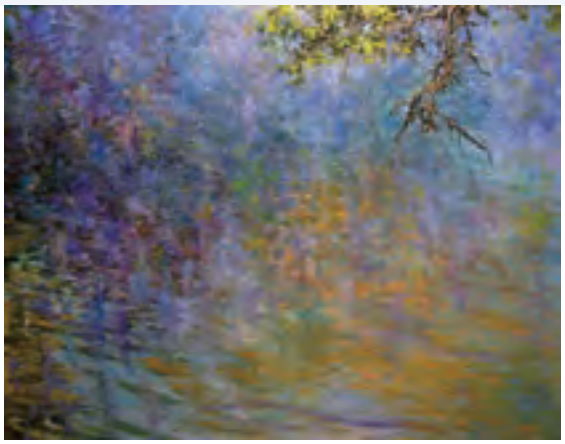
Secret Science Club inducts Alea Mills

With a growing audience of 400+ pushing the capacity of its Brooklyn bar venue, the Secret Science Club lecture series is no longer a secret! Professor Alea Mills is the latest CSHL investigator to take the stage at the monthly gathering. Previous CSHL lecturers have included Drs. Stillman, Hannon, Martienssen, and Mitra. More evidence that the secret is out: a glowing article on the club in the *New York Times*, in which one loyal attendee explains it began in 2006 as "push-back" against "national stupidity." The idea that "people were sick of being dumb" might have been key to success of the science series, according to the *Times* piece. The Club's organizers have held steadfast to their original mission of keeping the barriers to the audience as low as the qualifications of the speakers are high: attendance is always free. Check it out: www.secretscienceclub.blogspot.com

2012 WSBS honorary degree to Sir Kenneth Murray

At this year's commencement convocation a distinguished scientist, Dr. Kenneth Murray, was awarded an honorary doctorate. Professor Murray, who was knighted by the Queen of England in 1993 for his discovery of Hepatitis B antigens, graduated with a degree in chemistry from the University of Birmingham in 1956. He received his Ph.D. in Chemistry on an accelerated track just 3 years later. His list of achievements includes developing a life-saving hepatitis vaccine, starting the first European biotech company and creating his own philanthropic organization — the Darwin Trust — to support biological sciences at the University of Edinburgh to train of scientists from less affluent parts of the world.

Faculty & Friends



Labapalooza

The CSHL Association's springtime fundraiser "Labapalooza" rocked the campus in April, raising $125,000 to support the Lab's young scientists working on cancer, autism, Alzheimer's, schizophrenia, Parkinson's and depression. Many of the scientists demonstrated hidden talents, performing in a range of musical genres throughout the evening. Local artist and association director David Peikon orchestrated an ensemble of acclaimed realist painters from across the country who generously donated proceeds of art sales to the Laboratory, including: Robert Armetta, Franco Castelluccio, Dennis Cheaney, Leeanna Chipana, Steve Forster, Edward Minoff, Catherine Prescott, Carlo Russo, Lori Shorin and Jackie Watson.

Explaining 'big' ideas about biofuels, genomics in the cloud

Visit www.bigthink.com to watch CSHL researchers Rob Martienssen and Michael Schatz (@mike_schatz on Twitter) explain how they're applying their research to solve some very big problems. Plant biologist Martienssen describes how he's using the principles of epigenetics that his group has uncovered to "persuade" a tiny weed to produce biofuel. Quantitative biologist Schatz talks about his efforts to modify Google's "secret sauce" to manage the DNA data deluge brought on by the revolution in genome sequencing.

Genetics Society of America honors DNALC's David Micklos

Founder and executive director of CSHL's DNA Learning Center (DNALC) David Micklos is no stranger to awards that honor innovation in science education. The latest is the 2012 Elizabeth W. Jones Award for Excellence in Education by the Genetics Society of America (GSA). The award honors Micklos for bringing "the excitement of DNA science into the educational curriculum for thousands of students, high school teachers, and undergraduate faculty." The DNALC provides hands-on laboratory learning to more than 35,000 middle and high school students every year. Thousands of teachers nationwide have been trained in molecular biology to enhance their existing curriculum.

77th Cold Spring Harbor Symposium on Quantitative Biology

The Biology of Plants

May 30 - June 4, 2012

Abstracts due March 16, 2012

Speakers:

Rick Amasino, *University of Wisconsin. Madison*
Julia Bailey-Serres, *University of California, Riverside*
James Barber, *Imperial College London, United Kingdom*
Kathryn Barton, *Carnegie Institution of Science*
David Baulcombe, *University of Cambridge, United Kingdom*
Philip Benfey, *Duke University*
Frederic Berger, *Temasek Life Sciences Laboratory, Singapore*
Dominique Bergmann, *Stanford University*
Thomas Brutnell, *Donald Danforth Plant Science Center*
Vicki Chandler, *Gordon & Betty Moore Foundation*
Xuemei Chen, *University of California, Riverside*
Joanne Chory, *The Salk Institute for Biological Studies*
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Steven Jacobsen, *University of California, Los Angeles*
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Sophien Kamoun, *The Sainsbury Laboratory, United Kingdom*
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Olivier Voinnet, *Swiss Federal Institute of Technology Zurich, Switzerland*
Daniel Zamir, *The Hebrew University of Jerusalem, Israel*
Jian-Kang Zhu, *Purdue University*
Daniel Zilberman, *University of California, Berkeley*

Organizers:

Terri Grodzicker, Robert Martienssen,
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Cold Spring Harbor Laboratory

Topics:

- Stem Cells & Development
- Gametogenesis & Germ Cells
- Hormones & Signal Transduction
- Cell Division & Cell Cycle
- Regulatory RNAs
- Epigenetics
- Clocks & Rhythms
- Photosynthesis
- Genomics, Speciation & Evolution
- Stress Responses & Adaptation
- Molecular Ecology
- Host-Pathogen Interactions
- Symbiosis
- Metabolism & Biofuels

Registration, abstract submission and further information:
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Image credit: Pea plant 3D model by James Whitaker, based on drawings by Gregor Mendel, an Austrian monk whose breeding experiments with garden peas, in 1866, led him to formulate the basic laws of heredity.

Poster credit: Catherine Dougherty

Cold Spring Harbor Laboratory
Cold Spring Harbor, NY 11724

Upcoming events

JUNE 12 Tue | Cold Spring Harbor Laboratory's Golf and Tennis Tournament
Piping Rock Club, Locust Valley, NY

JUNE 26 Tue | Follow Your Genes — Decision Making and Your Personal Genome
Grace Auditorium, 7 PM

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