Of a scientific odyssey in which Nick has persisted in the face of doubters in the pharmaceutical industry. Tonks’ team has recently demonstrated their ability to target PTP1B—with a drug Nick developed years ago—in cellular signaling pathways that play a key role in HER2-positive breast cancer. Phase 1 trials will begin at Northwell in the spring of 2016. Other PTP1B-targeting compounds in Tonks’ lab are being evaluated by a major pharmaceutical firm for treatment of diabetes and obesity. It’s another illustration of how basic science can pay off in ways that are not contemplated at the outset. We see similar promise in other fields: for instance, in Zachary Lippman’s basic research on the process of branching morphogenesis in plants, which now points to a way of significantly increasing fruit yields; and in Steven Shea’s fundamental research on social behavior in rodents, which has led to unexpected insights into Rett syndrome, an autism spectrum disorder.

Basic research has made all of these opportunities possible. To keep our discovery science robust, we were pleased this past year to have been asked to join the ranks of select institutions named as beneficiaries of the Scientific Philanthropy Alliance. The SPA serves as an impartial advisor to major philanthropists, promoting basic research as the driver of new ideas, of new economic wealth and for the education of a new generation of talented new scientists. Several benefactors of the Laboratory organized the SPA, which we thank for providing another line of support for the basic research that is the lifeblood of Cold Spring Harbor Laboratory.
CANCER
Researchers at CSHL are devoted to understanding the fundamental biology of human cancer. Their commitment to studying basic cellular processes reflects the premise that understanding how these processes are altered in cancer cells will provide a framework for rational therapies. Several technological advances developed at the Laboratory have given rise to innovative genomic approaches and the development of new mouse models of various cancer types. These provide a powerful pathway for discovery, characterization, and validation of genes that contribute to cancer development and progression. A unique aspect of the CSHL cancer program is its cooperative nature. Scientists are encouraged to share their ideas and work on questions across labs, in a synergistic way that far exceeds the power of any single laboratory working in isolation. CSHL has been designated as a Cancer Center of the National Cancer Institute since 1987.

NEUROSCIENCE
CSHL neuroscientists focus on understanding how neural activity and neural circuitry underlie behavior, and how disruptions in these circuits lead to neurological and neuropsychiatric disorders such as Alzheimer’s disease, autism, schizophrenia, and depression. These questions are addressed in two model systems—rodents and fruit flies—using molecular, cellular, genetic, developmental, theoretical, physiological, and behavioral approaches. Neuroscience research at CSHL is highly collaborative and can be divided into three broad themes: sensory processing, cognition, and cognitive disorders. In addition, there is an effort to develop new anatomical methods to improve our understanding of brain circuits, connectivity, and function.

PLANT BIOLOGY
The plant group at CSHL studies fundamental mechanisms in plant development and genetics that impact crop productivity, biodiversity, climate change, and the development of biofuels. Their research uses Arabidopsis, maize, and most recently tomato as model systems, and it expands upon the Nobel Prize−winning work done at CSHL by Barbara McClintock in the 1940s and 1950s. The transposable genetic elements, or “jumping genes,” that she discovered are now understood to reprogram the epigenome and are being used at CSHL for functional genomics in Arabidopsis and maize. CSHL has taken part in numerous plant genome-sequencing projects including Arabidopsis, rice, sorghum, and maize, as well as epigenomic sequencing and profiling.

GENOMICS
The Genomics Program is composed of faculty working across disciplines and research areas. Its main research interests are genomic organization; structural variation of the human genome as related to disease; computational genomics and transcriptional modeling; and sequencing technology. Program facilities are located at the main campus and a few miles away at the Woodbury Genome Center. The investigators conduct research in the areas of human genetics, functional genomics, small RNA biology, and bioinformatics.

QUANTITATIVE BIOLOGY
CSHL’s Simons Center for Quantitative Biology (SCQB) brings to questions in biological science the insights of applied mathematics, computer science, theoretical physics, and engineering. Members of the SCQB interact closely with other CSHL researchers and apply their approaches to research areas including genomic analysis, population genetics, neurobiology, evolutionary biology, and signal and image processing.

RESEARCH ACTIVITIES

Dina Florin Albeau
Gurinder Atwal
Anne Churchland
Camila dos Santos
Joshua Dubnau
Mikala Egeblad
Grigori Enikolopov
Douglas Fearon
Hiroyasu Furukawa
Jesse Gillis
Thomas Gingeras
Christopher Hammell
Molly Hammell
Gregory Hannon
Z. Josu Huang
Ivan Issifov
David Jackson
Leemor Joshua-Tor
Adam Kepecs
Justin Kinney
Alexei Koulakov
Adrian R. Kraimer
Alexander Krarsnit
Je H. Lee
Dan Levy
Bo Li
Zachary Lippman
Gholson Lyon
Robert Martienssen
W. Richard McCombie
Alea A. Mills
Partha P. Mitra

Pavel Osten
Darryl Pappin
Scott Powers
Michael Schatz
Stephen Shea
Jason Sheltzer
Adam Siepel
Raffaella Sordella
David L. Spector
Arne Stenlund
Bruce W. Stillman
Marja Timmermans
Jessica Tollkuhn
Nicholas Tonks
Lloyd Trotman
Glenn Turner
David Tuveson
Christopher Vakoc
Linda Van Aelst
Doreen Ware
Michael Wigler
Anthony Zador
Lingbo Zhang
Hongwu Zheng
Yi Zhong

RESEARCH INVESTIGATORS
In 2015 Cold Spring Harbor Laboratory celebrated its 125th year. Today, CSHL is renowned for its research in Cancer, Neuroscience, Plant Biology, Quantitative Biology and Genomics. Scientists at the Laboratory work together, frequently across disciplines, to solve biology’s most challenging problems. This collaborative spirit as well as the scope of the faculty’s research interests are suggested in this sample of a few of the past year’s important findings.

**RESEARCH HIGHLIGHTS**

### Biomarker for treatment-resistant prostate cancer

In 2015 a new animal model for prostate cancer called RapidCap emerged from Lloyd Trotman’s lab. It is the only model in mouse in which the cancer metastasizes to the bone. This is precisely what happens in advanced metastatic prostate cancer. It is crucial to have such a model, since patient responses to hormone therapy vary widely, and it’s still unclear why some types of prostate cancer seem to be resistant to the therapy. Those cases that resist therapy—a minority—are liable to become metastatic. Crucially, Trotman’s model may help us determine which ones. His team has been using this system to trace the mechanisms underlying metastatic lesions. So far they have discovered that such lesions are very different from primary tumors in the prostate. Their work has shown that these metastases activate a pathway that involves the interleukin-6 (IL-6) protein, which activates the MYC oncogene that is expressed specifically in therapy-resistant metastatic prostate cancer cells. Using the IL-6 marker or associated proteins to predict which patients would benefit from hormone therapy would be a major advance. The hope is that translating the IL-6 discovery into clinics could help stratify patients into good responders and bad responders.

### Cholinergic warning system

In experiments with mice, Adam Kepecs and colleagues discovered a set of dedicated neurons in the basal forebrain that broadcast messages throughout the cerebral cortex, rapidly informing multiple distributed subregions of any surprising rewards or punishments. The neurons are cholinergic—they send signals in the form of the neurotransmitter acetylcholine. Such neurons are thought to play an important role in arousal, attention and learning, yet their precise role in behavior has remained mysterious, in part because of the technical difficulty in recording from them in vivo. Degeneration and loss of cholinergic neurons in the basal forebrain have been implicated in Alzheimer’s disease, age-related cognitive decline, and other cognitive disorders and dementias. Kepecs’ team showed how central cholinergic neurons function, using optogenetic methods as mice performed behavioral tasks that involved rewards or unexpected mild punishments. To explain their responses the team constructed a computational model which revealed that the modulation of signal strength was proportional to how unexpected or surprising the mice found the reward or punishment. According to the model, if the mice were confident their response was correct, the reward generated a weak signal. But if they were unsure, the reward came as more of a surprise and generated a stronger cholinergic signal. Kepecs suggests that cholinergic broadcasts to the cortex would be useful in boosting plasticity, allowing flexibility in neuronal connections that makes learning possible. Whether a surprise is positive or negative, the fact that it is unexpected, and the degree to which it is, would be an obvious advantage to the individual.

### Organoids to aid pancreatic cancer research

All cancer research relies on a steady supply of cells, both normal and cancerous, that can be grown in the laboratory. By comparing normal cells to cancer cells, scientists can identify changes that lead to disease. Yet both types of pancreatic cells have been difficult to culture in the laboratory. Another problem in studying pancreas cancer is the fact that many patients when diagnosed are already beyond the point at which surgery is an option. In concert with the Tuveson lab, Hans Clevers, a neighboring or “downstream” neuron, but also recruits a third neuron to inhibit the downstream target after some delay. They will now use a genetic mouse model of schizophrenia to determine if there are any noticeable changes in the observed feedforward inhibition in the thalamus–PFC pathway; these in turn might suggest novel targets for next-generation schizophrenia therapeutics.

In this coronal view of mouse brain, red fluorescence is generated by inhibitory neurons in the PFC, it illuminates any neurons providing input into them—implying a direct connection with red-labeled neurons in the thalamus. The team used optogenetic stimulation, a technique in which neurons expressing a light-sensitive protein are controlled with pulses of light, to observe a process called feedforward inhibition, a mechanism in which one neuron excites another neuron, but also recruits a third neuron to inhibit the downstream target after some delay. They will now use a genetic mouse model of schizophrenia to determine if there are any noticeable changes in the observed feedforward inhibition in the thalamus–PFC pathway; these in turn might suggest novel targets for next-generation schizophrenia therapeutics.

A pancreatic organoid grown in the Tuveson lab.

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How a brain circuit controls fear

It is hard to imagine that an intangible emotion like fear is encoded within neuronal circuits, but Bo Li and colleagues have discovered that fear is stored within a distinct region of the brain. In recent years, they have observed that fear learning and memory are orchestrated by neurons in the central amygdala. Now, Li, along with CSHL collaborators Josh Huang and Linda van Aelst, took on the question of what controls the central amygdala. They focused on a cluster of neurons that form the PVT, or paraventricular nucleus of the thalamus. This region is extremely sensitive to stress, acting as a sensor for both physical and psychological tension. The team found that the PVT is specifically activated as animals learn to fear or as they recall fear memories. They were able to see that neurons from the PVT extend deep into the central amygdala. Disrupting the connection significantly impaired fear recall fear memories. They were able to see that neurons in the central amygdala.

The team used data from people with post-traumatic stress disorder to discover that the well-known neural growth molecular mechanisms that connect the two structures, the PVT to the central amygdala. They postulated that the PVT is sensitive to stress, acting as a sensor for both physical and psychological tension. The team found that the PVT is specifically activated as animals learn to fear or as they recall fear memories. They were able to see that neurons from the PVT extend deep into the central amygdala. Disrupting the connection significantly impaired fear recall fear memories. They were able to see that neurons in the central amygdala.

Most effective druggable targets for cancer cells, across different cancer types and subtypes.

Our probabilistic approach to numbers

Humans, including pre-verbal babies and adults in indigenous cultures with no formal mathematical education, are capable of estimating numbers of objects. Yet while areas of the brain have been identified that respond to specific numbers, it has been unclear how numbers are represented. Scientists have generally assumed that the brain represents numbers of objects as single, whole values, or “scalars.” However, estimates of many other features of the environment—such as object depth, height and location—have been shown to be “probabilistic,” represented as a range of values. In 2015 Anne Churchland and colleagues reported results of an experiment combining auditory and visual cues to test whether people have a scalar or probabilistic sense of numbers. They determined that even a distinct number of objects in the world may be represented in the brain not as a single value but as a range of possible values. Subjects could perform an audio-visual task involving a numerical determination with any of three strategies. Some employed only the most reliable piece of information; others combined auditory and visual information to arrive at an estimate; still others randomly picked one piece of information on which to base their number estimate. These results have important implications for how we learn and understand our world. Representing numbers as a range of possible values allows people to utilize multiple streams of information, leading to improved decisions.

Reversibility of Rett syndrome symptoms

Another example of collaborative science at CSHL is newly published among investigators working in the three labs. They realized there might be some benefit in applying to a mouse model of Rett syndrome some of the work that’s been done in the Tonks lab in developing small molecule drugs that inhibit an enzyme called PTP1B, which Tonks discovered 25 years ago. Realizing that metabolic regulation appears to be abnormal in Rett syndrome—a largely unappreciated fact—Navasona Kinman, a Research Associate who works with Tonks, proposed using inhibitors of PTP1B to see if they might address any of the range of symptoms seen in the disease. He first demonstrated that PTP1B levels were abnormally elevated in the mouse model. This was an encouraging sign that inhibitors of PTP1B might have a beneficial effect. More exhaustive experiments with several candidate small molecule inhibitors demonstrated that they can significantly extend lifespan in male mice that model Rett syndrome and can ameliorate several behavioral symptoms of the disorder in female mice. This was tantalizing evidence that Rett symptoms can actually be reversed, and supports the concept that the disorder may be amenable to treatment with small molecule drugs—an objective the team continues to vigorously pursue.

Fine-tuning plant growth to optimize fruit size

A wonderful example of basic science having an important societal impact is work from Zach Lipson’s laboratory. His discoveries in recent years have identified among investigators working in the three labs. They realized there might be some benefit in applying to a mouse model of Rett syndrome some of the work that’s been done in the Tonks lab in developing small molecule drugs that inhibit an enzyme called PTP1B, which Tonks discovered 25 years ago. Realizing that metabolic regulation appears to be abnormal in Rett syndrome—a largely unappreciated fact—Navasona Kinman, a Research Associate who works with Tonks, proposed using inhibitors of PTP1B to see if they might address any of the range of symptoms seen in the disease. He first demonstrated that PTP1B levels were abnormally elevated in the mouse model. This was an encouraging sign that inhibitors of PTP1B might have a beneficial effect. More exhaustive experiments with several candidate small molecule inhibitors demonstrated that they can significantly extend lifespan in male mice that model Rett syndrome and can ameliorate several behavioral symptoms of the disorder in female mice. This was tantalizing evidence that Rett symptoms can actually be reversed, and supports the concept that the disorder may be amenable to treatment with small molecule drugs—an objective the team continues to vigorously pursue.

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Lippman and colleagues identified a set of genes that control stem cell production in tomato. Mutations in these genes explain the origin of mammoth beefsteak tomatoes. More important, the research suggests how breeders can fine-tune fruit size in potentially any fruit-bearing crop, a significant advance for agriculture. The secret of the beefsteak tomato, the team showed, has to do with the number of stem cells in the plant’s growing tip, called the meristem. They traced an abnormal proliferation of stem cells to a naturally occurring mutation that arose hundreds of years ago in a gene called *CLAVATA3*. Selection for this rare mutant by plant cultivators is the reason we have beefsteak tomatoes today. Lippman’s team examined never-before-studied mutant tomato plants, three of which contained faulty genes encoding enzymes that add sugar molecules to proteins. Their experiments revealed that the enzymes, called arabinosyltransferases (ATs), add sugar molecules called arabinoses to *CLAVATA3*. By adjusting the number of sugars on *CLAVATA3* proteins, and through other mutations affecting components of the pathway, Lippman and colleagues show it is possible to fine-tune growth in ways that could allow breeders to customize fruit size.

**Overcoming bad karma**

Epigenetics pioneer Rob Martienssen, whose discoveries confirm and extend the observations and predictions of CSHL Nobel laureate Barbara McClintock, this year solved a 30-year-old mystery that had cost growers of the oil palm tree hundreds of millions of dollars in ruined crops. In the 1980s, a new method of generating plantations brimming with clones of the highest-yielding specimens of the oil palm plant met with unanticipated disaster. Corporate investors were astonished to observe that the finest hybrids, cloned in culture dishes, often grew into barren adults bearing desiccated, worthless fruits. These plants displayed a mutant form that scientists called “mantled.” Martienssen’s work, aimed at more completely understanding how epigenetic mechanisms influence and even control plant development and evolution, traced the problem to a transposable element lodged within the oil palm gene called *MANTLED*. This “jumping gene” is an example of the myriad genomic invaders that lay (mostly) dormant within and between genes in all forms of life. This particular invader, or one very similar to it, was first spotted in rice plants, and had been named *karma*. Martienssen and colleagues discovered that in mantled plants, a methyl mark present in healthy plants was missing at a location in *karma* called a splice site. When the splice site is unmethylated, the RNA message copied from the gene encodes a mutant protein that gives rise to plants with worthless fruit. A simple epigenetic test will readily identify bad *karma* and thus enable growers to cull damaged clones at the plantlet stage. It will promote the propagation of healthy high-value hybrid clones and thus reduce the economic pressure on growers large and small to devote additional tropical rainforest territory to oil palm cultivation.