COLD SPRING HARBOR LABORATORY
Spring 2009 • Volume 29 • Number 1

HARBOR TRANSCRIPT

The thrill of discovery

The Harlem DNA Lab opens

PRESIDENT'S MESSAGE

Many people still believe that science moves forward in great leaps, the result of epoch-altering discoveries made at intervals of many years by great men working in isolation. No one can be blamed for holding on to this romantic (not to mention gender-biased) notion of the way science works. The image has been burnished in the popular imagination by countless portrayals in mass media. Yet the truth about science and scientists is even more interesting, and even more remarkable. We have evidence of this in the work performed every day at Cold Spring Harbor Laboratory.

Science moves forward constantly and in increments usually so small as to fall beneath the threshold of media attention. Our progress is by no means routine, but it is unrelenting and inexorable. This, despite short-term challenges ranging from the conceptual to the technological to the fiscal. The current year is one whose challenge is expressed in the language of dollars and cents, pounds, euros, and yen. The global economy has contracted, and this affects our work at the cutting edge, where experiments and experimenters don't come cheaply. But the recent downturn will not stop our progress. It cannot.

Science in the 21st century is a profoundly collaborative and cross-disciplinary enterprise, involving men, and at long last women, of all races and ethnicities. It's probably the best example of cooperation across artificially drawn lines of division that humankind has yet produced. This fact is a great source of strength and a prime reason for optimism. Another concerns the human spirit itself, which constantly fuels our curiosity and powers our engines of discovery. The work of Dr. Tom Gingeras, whom we welcome back to CSHL after two productive decades at Affymetrix, is described in these pages. Tom and colleagues in the ENCODE project are literally redefining the genome — but doing so one small step and one incremental discovery at a time. No one yet knows the outcome of this work, and no can possibly know. That's the beauty of science, which will move forward against any impediments, because Tom and Linda Van Aelst — another outstanding CSHL investigator featured in these pages — like scientists everywhere, will continue to seek enlightenment.

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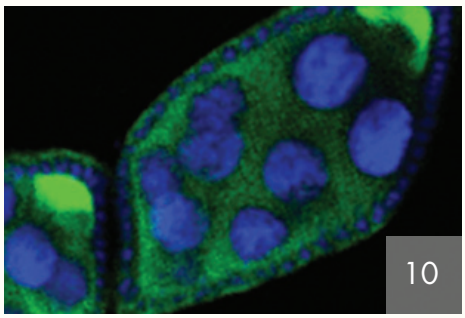


FEATURES

FACULTY & FRIENDS

On the cover:
Orubba Almansouri, who emigrated to the U.S. from Yemen only two years ago, preparing a sample of her own mitochondrial DNA at the new Harlem DNA Lab. She is the student body president at Brooklyn International H.S. "In my country," she says, "the public schools were always very crowded, maybe 80 students per class. The girls were separate from the boys. We didn't do labs."

The Harlem DNA Lab opens

Bringing CSHL's educational vision to nation's largest public school system

The students shown in this story — 30 recent immigrants to the U.S, all well on their way to mastering English — are from Brooklyn International H.S. This was their first chance to extract and analyze their own mitochondrial DNA. Their countries of origin: Yemen, Tibet, China, Haiti, Guinea, Congo, Dominican Republic, Nepal, Bangladesh, Mexico.

Last fall, at the very beginning of the 2008–09 school year, the ribbon was cut on a gleaming new Harlem DNA Lab. The facility, full of state-of-the-art equipment, occupies a 1,200-square-foot former graphics workshop in the John S. Roberts Educational Complex, the site of a junior high school on First Avenue at 120th Street in Manhattan. For CSHL, the Harlem Lab is the most vivid fulfillment to date of a democratic vision of science education articulated by David Micklos and others at the Laboratory over the last 20 years:

> *We envision a day when all elementary students are exposed to principles of genetics and disease risk; when all high school students have the opportunity to do hands-on experiments with DNA; and when all families have access to genetic information they need to make informed healthcare choices.*

Since 1988, over 325,000 school children, parents and teachers have visited the Dolan DNA Learning Center (DNALC), located in the town of Cold Spring Harbor, while some 8,000 additional teachers have received training at DNALC workshops conducted in 42 states and several foreign countries. All have experienced the thrill of performing simple yet impressive experiments with DNA — often their own, extracted and amplified using methods that genome scientists employ daily in laboratories worldwide.

In his remarks at the Harlem Lab's opening, Dr. Bruce Stillman, CSHL president, explained the importance of this aspect of CSHL's educational mission, which, in its other phases, addresses the needs of undergraduates, graduates, postgraduates, and the professional education of practicing scientists.

"Biology is happening right now, and shouldn't be taught as a chapter of a history book," he said. "It's perhaps the fastest moving field of scientific research, and will be a prime factor influencing improvements in healthcare in our immediate and more distant future. It's also a formidable factor shaping our nation's economy. In view of this, we at CSHL have an obligation to bring the latest knowledge and cutting-edge tools and techniques in modern biology to the students of New York City, who number over a million — the largest body of public school students in the United States."

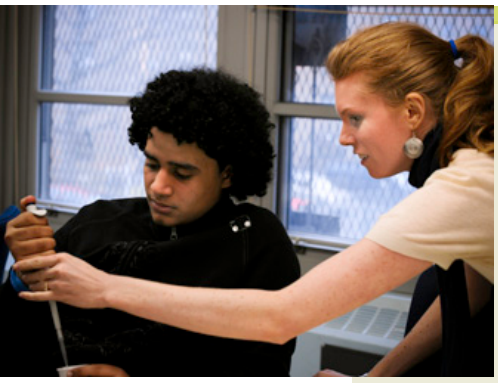
A busy first year

In its first two terms of operation, the Harlem DNA Lab already has hosted some 1,800 visiting students, spanning grades 6 through 12, most of whom come with their classes to conduct carefully planned half-day laboratory experiments. Four-fifths of these students attend schools serving predominantly minority neighborhoods, most of which lack lab equipment needed to perform comparatively sophisticated experiments involving DNA extraction and analysis. A collaboration of CSHL and the New York Department of Education, the Harlem Lab is supported by generous grants from HHMI, The Dana Foundation, Jerome L. Greene Foundation, The Goldman Sachs Foundation and William Townsend Porter Foundation.

A teacher's story

Sometimes life brings you full circle. I'm the daughter of a Puerto Rican mother and a Cuban father. I was born in Spanish Harlem and grew up on 116th Street, right around the corner from this school — these are students I can really relate to.

I have a love for biology that goes back to the summer of my 11th year, when my family moved to an old house in the South Bronx. On one of my exploratory trips to our dark basement I found a yellow tin locker with a small light microscope inside. I observed my first paramecia and other swirling organisms through that instrument, which set me on a course that led eventually to a Ph.D. in molecular biology and the beginnings of a career in research. My love for teaching brought me back to the South Bronx, where I taught for seven years, and later to a wonderful charter high school in upper Manhattan, whose students remind me of those visiting the Lab today. In this group alone we have students from 10 countries, many of them recent immigrants.



"The nice thing about having this lab in Harlem is that it's open to everyone. This program shows that all kids can profit from this experience, not just the honors students. More and more graduates are coming back to me and saying, 'Hey, it all began in your class.'"

— Kathleen Rucker
Brooklyn International High School

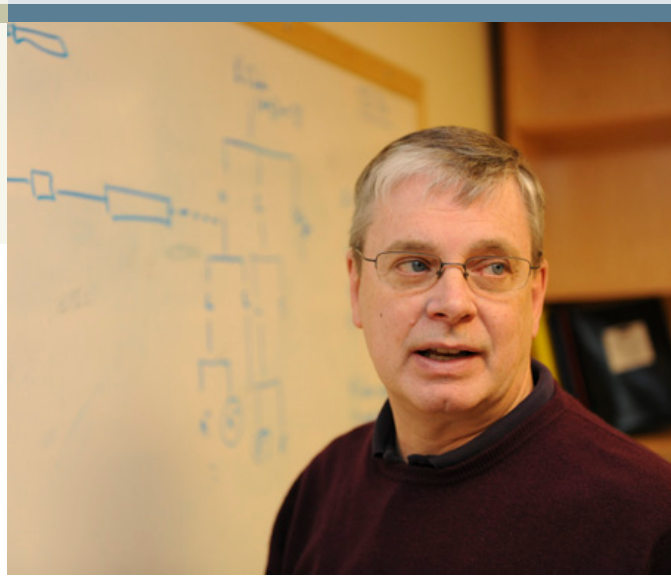
These students are from the Brooklyn International School. And the lab we're doing is a kind of metaphor for the concept behind The Harlem DNA Lab and the program that David Micklos has created over many years. The first thing we do, literally, is take the biology out of the textbook. We're all doing the same experiment together. And, as you can see, these 11th graders are immediately immersed. Their teachers have prepared them well. There is no training period; I talk them through the lab. It's all hands-on, and, after a little shyness at the very beginning, the kids plunge in — they're swimming in the deep water.

In today's lab, they're extracting a sample of their own mitochondrial DNA (mtDNA) and preparing it for analysis. This lab shows them one way in which each of us is different — each gets to see point mutations in their mtDNA that distinguishes them from their classmates. But this lab also shows them that in the final analysis, we are more alike than different. I help them put that personal discovery in the context of the current scientific debate over human origins. The exercise is partly about the scientific method and the role of evidence. But what's most touching to me is seeing kids have the same reaction I did as a kid — they see the lab equipment and are immediately drawn to it. Even when the work is done, they don't want to leave the lab!

— Ileana Rios, Ph.D.
Science Educator, Harlem DNA Lab

The gene, redefined

"Almost every part of the genome has a function, although in many cases we don't know the right context in which to appreciate what that function is."



A half-century ago, scientists in the young field of molecular biology figured they had a pretty good notion of how the genetic code operated. Back then, decades before the advent of genome sequencing, the human genome's 23 chromosomes were thought to harbor as many as one million distinct genes — each presumed to encode a single molecule of RNA, the template, it was then believed, for the synthesis of one protein. Proteins were understood to be the basis of most functions in the cell, including the regulation of genes themselves.

Fast-forward to 2001, the year in which biologists and computer scientists pieced together a draft sequence of the 3 billion pairs of chemical "bases," or nucleotides, that comprise the human genome. Among the first surprises was a preliminary gene count. There were not a million, not 100,000, not even 50,000; in the emerging consensus it appeared that the genome of *H. sapiens* contained fewer than 25,000 genes.

How could 25,000 genes give rise to a million distinct human proteins? Alas, the "one gene-one protein" orthodoxy had long since been overturned and replaced by a concept called alternative splicing, which explained how a single gene could generate many different RNA "messengers" and potentially, therefore, multiple proteins.

Alternative splicing is one of many phenomena that have complicated our notion of how the genome is organized and how its many elements function. Not long after the assembly of the draft human genome, a public research consortium called ENCODE (The Encyclopedia of DNA Elements) was launched by the National Human Genome Research Institute. Its aim: to compile a comprehensive list of functional elements across the human genome.

Tom Gingeras and the ENCODE "heresy"

Last summer, Thomas Gingeras, Ph.D., a widely recognized genome investigator and developer of pioneering technologies used to probe it (notably, DNA microarrays), formed a new lab at Cold Spring Harbor Laboratory. Among other things, Gingeras returned to the campus — he had headed a lab at CSHL from the late 1970s until the mid 1980s — to carry forward his work on ENCODE. As one of the consortium's five principal investigators, he has been in prime position to ponder the significance of data generated since the project's inception. Gingeras is straightforward in conceding that his interpretation of this data is nothing short of "heresy" in the eyes of many other genome scientists.

Details of the controversies arising out of ENCODE's preliminary results — a paper setting forth pilot-stage data appeared in *Nature* last fall — are frankly abstruse. In broad terms, however, it is not difficult to appreciate why they have caused a stir. In the eyes of Gingeras, the data supports a dramatically new definition of what it means to say an element of the genome is "functional." Equally surprising, the data tend to destabilize long-held assumptions, including what it means to label a stretch of the genome a "gene."

Following completion of the human reference genome, scientists who totaled up the "acreage" devoted to its 20,000-plus protein-coding genes reported a figure ranging from 1% to 2% of the genome. It became fashionable to consider the remaining 98% to 99% "junk DNA." If a sequence did not code for protein — i.e., if it was not part of a gene — it was assumed to perform no useful function.

Perhaps the chief "heresy" to arise out of ENCODE's data is this: nearly all of the genome, far from being "junk," appears to have some kind of function. In a series of papers published from 2002 through 2007, Gingeras and ENCODE collaborators, extrapolating from an analysis of 1% of the genome, concluded that an astonishing 94% of the human genome is

transcribed as RNA. The question is, What are all these RNA transcripts *doing* in cells? Are they in fact doing anything of biological importance?

That last question has a partial answer, thanks to the uncovering of a previously unknown species of RNA molecules called small RNAs. These short molecules, most of them 19 to 200 nucleotides in length, have been classified into a multiplicity of subsets, according to size and presumed function within cells (only a fraction of which are now grasped). Small RNAs have been given names that most people outside of biology will find unfamiliar, e.g., microRNAs (miRNAs), piwi-interacting RNAs (piRNAs), short interfering RNAs (siRNAs).

Gingeras estimates that several thousand different small RNAs operate in human cells. Thanks in part to discoveries by Greg Hannon and Leemor Joshua-Tor of CSHL, we now know that specific cellular machineries "slice" and "dice" non-protein-coding RNA transcripts. The products are small RNAs that act very selectively to silence gene expression, a mechanism called RNA interference, or RNAi.

The case of small RNAs helps shed light on Gingeras's view of "function" across the genome. He contends that a very long non-coding RNA transcript, many thousands of nucleotides in extent — which orthodoxy would consider non-functional since it does not code for biologically active proteins and is not conserved by evolution — should indeed be considered a functional genome element. Its only purpose may be to present the cell's various processing machineries with copious raw material from which to excise short RNA segments. A processed small RNA, though minuscule in size relative to the non-coding sequence it was cut from, is available to regulate the expression of a specific gene. If the small RNA is considered functional, then so should the giant non-coding RNA that gave rise to it, argues Gingeras.

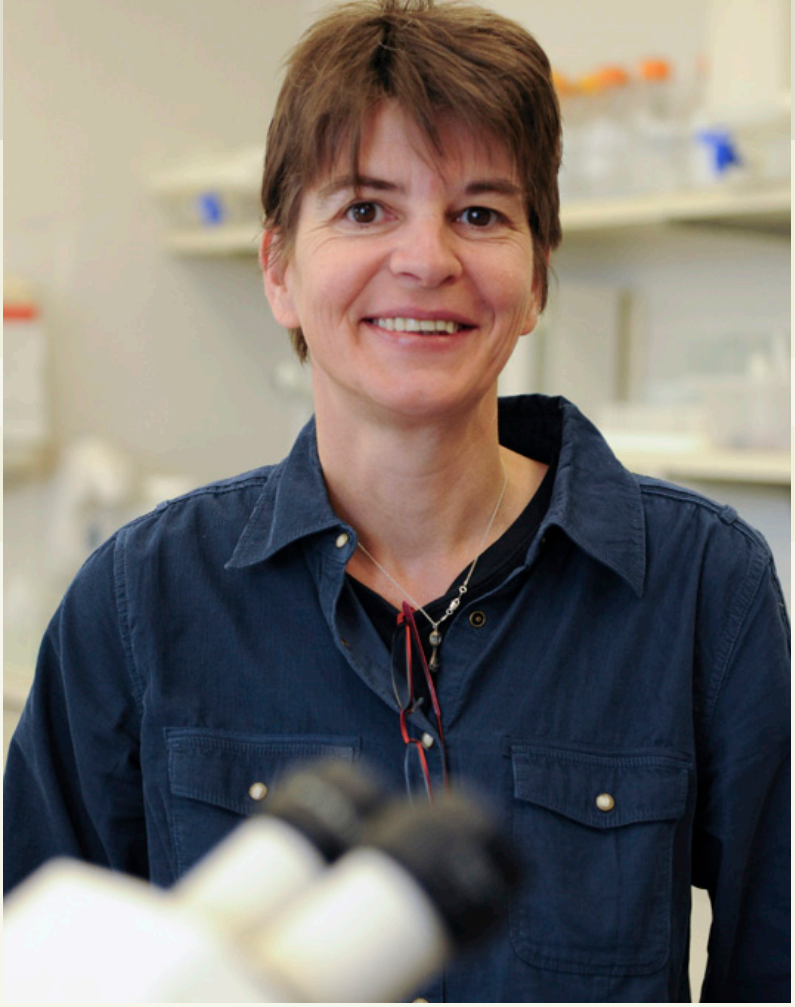
Gingeras wants his colleagues to think about what the genome looks like in what he calls "RNA space." In other words, from the perspective not of genes or proteins, but RNAs — the entire universe of them, protein-coding and non-coding. Using a computer, Gingeras has drawn a map that, in his words, "tells us what one of the human chromosomes looks like in RNA space." The representation of chromosome 21 looks as if it has been ripped from the notebook of a teenager playing with a compass and protractor. This abstraction of intersecting arcs bouncing off the sides of concentric circles brings to light two remarkable facts.

First, in many tissues, bits of DNA sequence associated with one gene are found inside the sequence of another gene. In some cases, a gene can be observed to "start" inside another gene; but, if its sequence is spatially scattered in this manner, how then does one define the gene? Where are "genes" located if they start or stop inside other genes, which have their own presumed start and stop points? And what to make of the latter when parts of their own sequence may also be dispersed in the space of other presumed "genic regions"?

The other unexpected insight: there are many examples on chromosome 21 of genes widely separated but whose RNA products, when meticulously traced, are shown to be mixed together. Bits of one non-coding RNA transcript are found inside another. In RNA space, in other words, a network of interaction is implied among gene products that one would otherwise have no reason to believe to be associated.

ENCODE data supports a view of the genome that "is so much more complex" than prevailing models that resistance is inevitable; "I expect people will gradually accept our data, but I also expect more arguments about the semantics of what 'functional' really means," says Gingeras. "I can only carry on with my work, and be content that the field will follow where the evidence takes us."

Linda Van Aelst



Cell Signaling Opens a Window on Cancer and Brain Disorders

For almost 20 years, Linda Van Aelst has been eavesdropping on Ras-driven chatter in cells of various types, starting with the humble, single-celled yeast and moving all the way up the chain of complexity to various mammalian cell types, including nerve cells found in the brains of mice and rats. By understanding how certain messengers and their messages go awry, she hopes to find ways to restore normal communication in cells that have either strayed down the road to cancer or gone out of sync to give rise to cognitive disorders like autism and mental retardation.

Van Aelst first encountered the Ras protein as a graduate student at Belgium's Catholic University Leuven, one of the oldest universities in Europe. Growing up in Flanders, she had dreamed of becoming either an archeologist or a biologist. "I've always been eager to do a job in which I would discover something new," she says. "Initially, it didn't matter whether I acquired information about the past, present, or the future, as long as it was novel. But eventually, biology won out."

In grad school she began reading reports that described events in cells in which the Ras protein had become mutated. The burning question of the moment: "How did a mutation in the gene that codes for the production of Ras turn normal cells into cancer cells?"

Mutations in three different *ras* genes can be found in roughly one-third of human cancer samples. In some tumor types, the number can be as high as 90%. Although ras was found to be an oncogene back in the early 1960s, scientists were still scrutinizing the cell's networks to identify how the Ras protein interacted with so-called downstream partners.

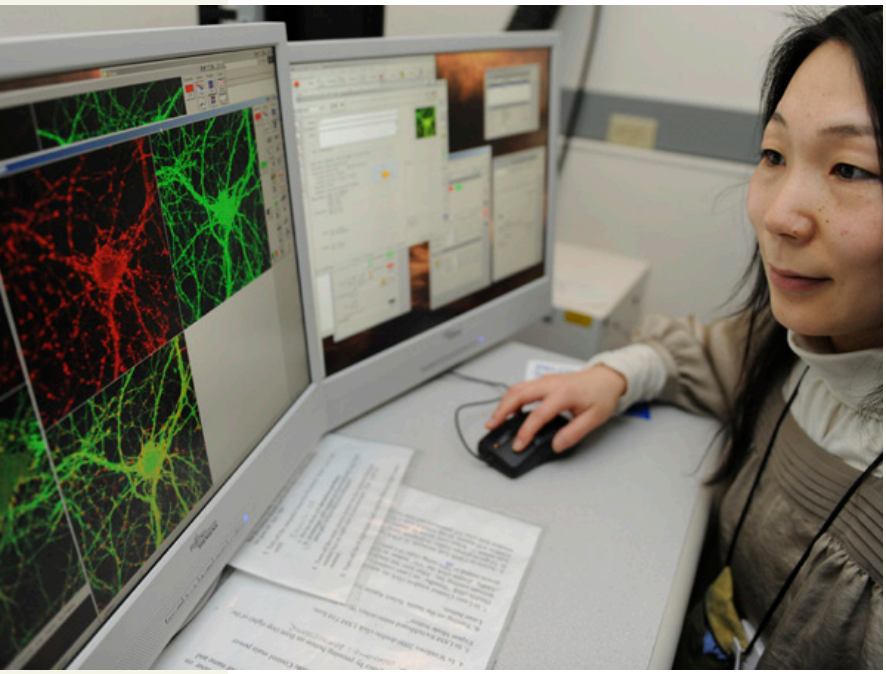
A protein called Ras

Our bodies function properly only because each of our cells is an expert in communication. Cells numbering in the trillions are engaged in a constant talkathon in which scores of molecules take part in signaling networks. These networks pass along messages in the form of chemical reactions that activate, suppress, and modify every aspect of the cell's life and function.

Prominent among these molecular signal transmitters is a protein called **Ras**. Along with other members of an extended "superfamily," Ras participates in what resembles a cellular version of the "telephone" game, whose outcome influences most major cell activities including growth, division, migration, adhesion, and, inevitably, death. So it's no surprise that when Ras and its relatives malfunction — by being too active, acting out of turn, getting messages wrong, or not sending them at all — the cellular mayhem that ensues results in disease of various kinds, many of them potentially catastrophic.

"I've always been eager to do a job in which I would discover something new."

LINDA VAN AELST



"We still don't know precisely what the relevant molecules and signaling pathways are for any given type of cancer," says Van Aelst. "This is the kind of information that will help in the design of better, targeted drugs."

The research papers that most excited grad student Van Aelst came from across the Atlantic, from the laboratory of an investigator at Cold Spring Harbor Laboratory named Michael Wigler, who was trying to piece together the daisy chain of proteins that worked downstream of Ras. Meeting Wigler at a scientific conference in Madrid in 1991, Van Aelst had a chance to question him closely about his work.

Above: Postdoc Akiko Kobayashi examines the effect of loss of oligophrenin-1 on the activity of nerve cells in the rat brain.

Facing page: Fruit fly experiments have led postdoc Benjamin Boettner to discover how Rap signaling controls cell shape during growth and movement.

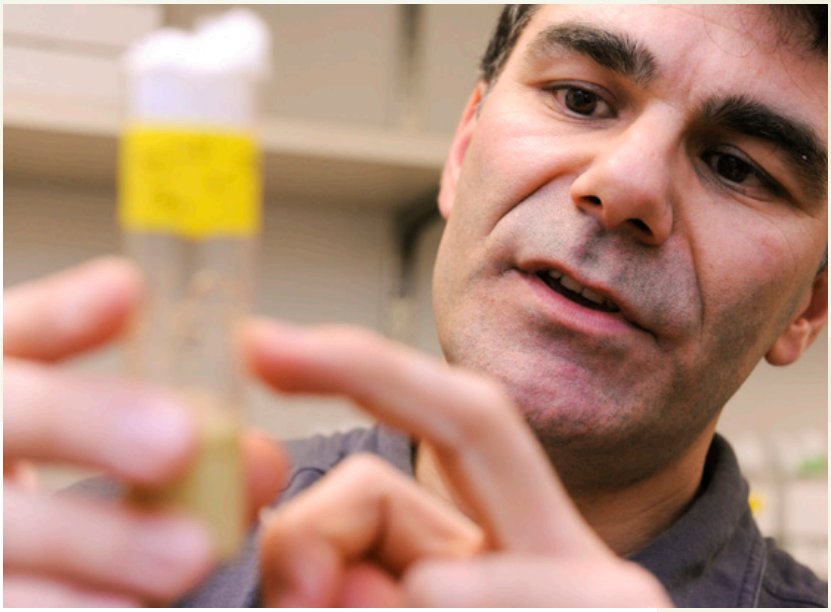
Problems with Ras can lead to cancer

A year or so later, with her doctorate in hand, Van Aelst arrived in Wigler's lab at CSHL for postdoctoral training. Her hunt for Ras's partners produced a quick payoff. Identifying and describing the physical interaction between Ras and another oncoprotein called Raf, her work indicated an important link to a well-known oncogenic network that also involved proteins called MEK and MAP kinases.

Protein kinases are enzymes that modify target proteins by adding phosphate groups to them. Such modifications are an excellent example of the abstract language through which signals are passed along in cells. Ras acts to control "downstream" target proteins by acting as a molecular on/off switch.

When Ras is bound to a protein called GTP, it acts as an "on" switch for the pathway. But once GTP is converted to another protein called GDP, the switch is turned "off." Under normal conditions, Ras and other so-called "GTPases," have to continually cycle between "on" and "off" states to keep the downstream signaling network humming along smoothly.

Van Aelst and colleagues in the Wigler lab showed how gene mutations that lock GTPases in the "on" state can lead to signal distortions causing cells to become cancerous. With her postdoctoral training coming to an end, she mulled a job offer that would have allowed her to return to her native Belgium and a permanent position at the renowned Ludwig Institute. But Wigler and Jim Watson suggested that she stay on at CSHL and start up her own group. Once established at the Laboratory, Van Aelst devoted some of her attention to "relatives" of Ras, including proteins called Rac and Rho. These molecules control pathways that help determine cells' shape, movement and communication. As Van Aelst inched into this new field using new model systems, there were indications that mutations in Rho-associated proteins might be involved in cancer metastasis.



Branching out into neuroscience

All the while, Van Aelst was well aware of research demonstrating the role of Rho proteins in the development of nerve cells in the brain. In the early 2000s, a growing number of mutations associated with Ras and Rho family members and the enzymes that control their activity were found in people suffering from disorders such as autism, neurofibromatosis, and X-linked mental retardation. Van Aelst was especially intrigued to note that some of these proteins were molecules she had identified as Rho's partners in her yeast experiments years earlier.

"It was a good time to expand into a brand new research area," she recalls of the days when she began to educate herself about neuroscience. "It was a big challenge to set up totally new technology to do experiments in a new field. I just had to take a deep breath, expel my fears and go for it."

With Robert Malinow's lab, Van Aelst discovered that Ras and Rap proteins play critical roles at synapses, the tiny junctions across which brain cells communicate. Specifically, they help establish synaptic plasticity — critical changes in the strength of the connection and likely a basis of learning and memory. With Holly Cline, she discovered that different Rho GTPases regulate distinct aspects of the development of dendrites — the tree-like branching structures found at the ends of neurons that receive signals from other neurons. More recently, the lab has been focusing on a gene called *oligophrenin-1*, which inactivates Rho (see box below).

As deeply entrenched as she is now in studying how Rho GTPase signaling shapes the workings of the brain, Van Aelst hasn't forgotten her cancer-biology roots. With funds from the National Cancer Institute, she is actively pursuing the mechanism by which a signaling "adaptor" called Dok-1 slows down the progression of leukemia and how Ras-related proteins control so-called cell adhesion complexes that are important in tumors.

Far from being a distraction, Van Aelst finds that applying her expertise in two different fields is enriching. "I feel like it has made me more open-minded," she says.

Studying a gene linked to mental retardation

Oligophrenin-1 is one of the genes mutated in people with X-linked mental retardation. In 2004, the Van Aelst team used RNA interference — a technique that silences genes — to "knock down" the expression of this gene in samples of rat brain — thus mimicking the illness in people. Their work showed that *oligophrenin-1* was essential for neurons to develop tree-like dendritic structures of the correct shape and size.

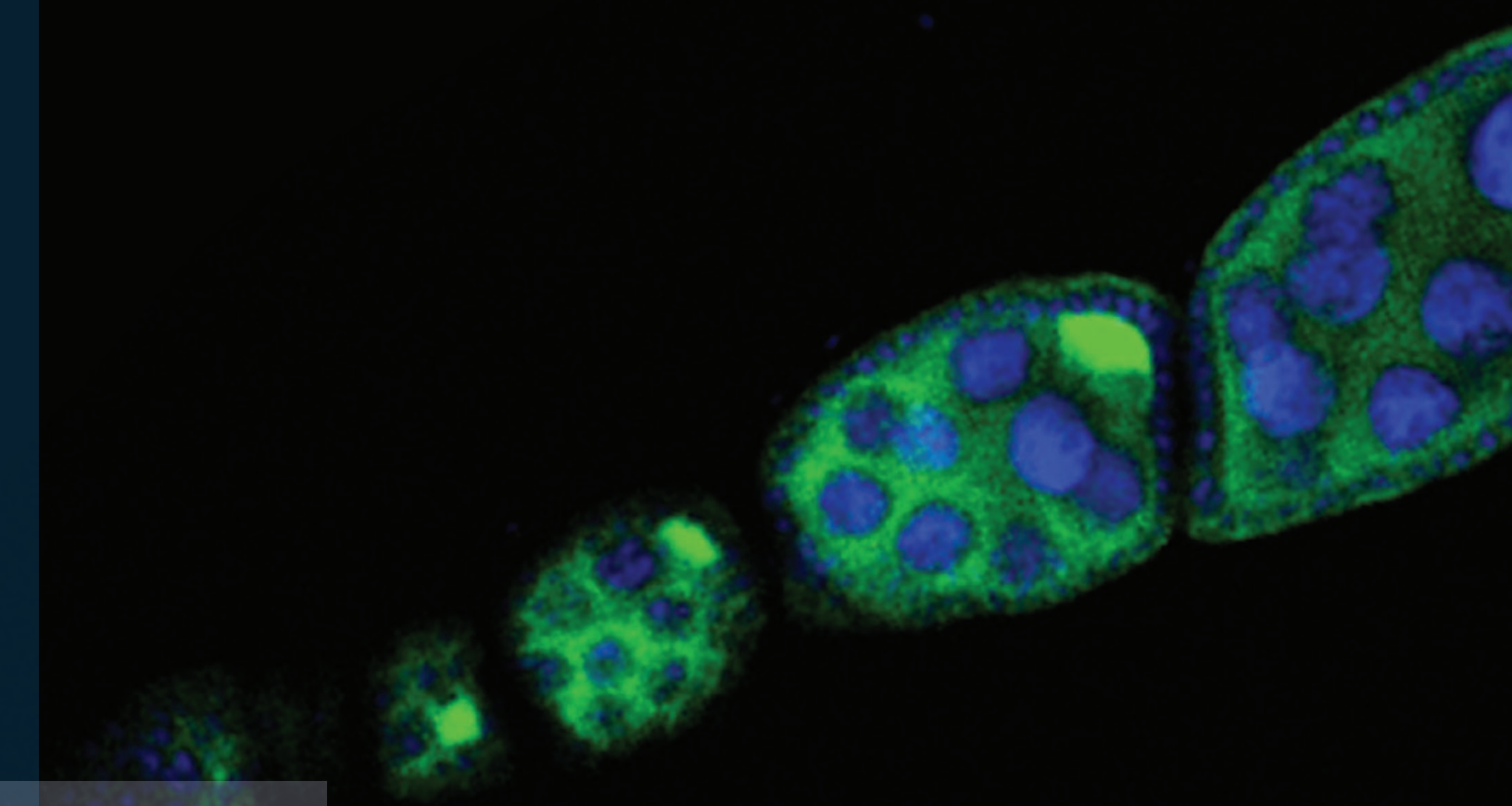
More recently they have shown that the protein made by this gene also seems to play a role in the maintenance of synaptic structure and plasticity. Plasticity refers to the strength of the connection between two neurons. Changes in plasticity are a known basis of brain functions such as learning and memory. By acting on both sides of the synapse, oligophrenin-1 seems to support long-lasting strengthening in the communication between two simultaneously stimulated neurons that is thought to underlie long-term memory formation and learning.

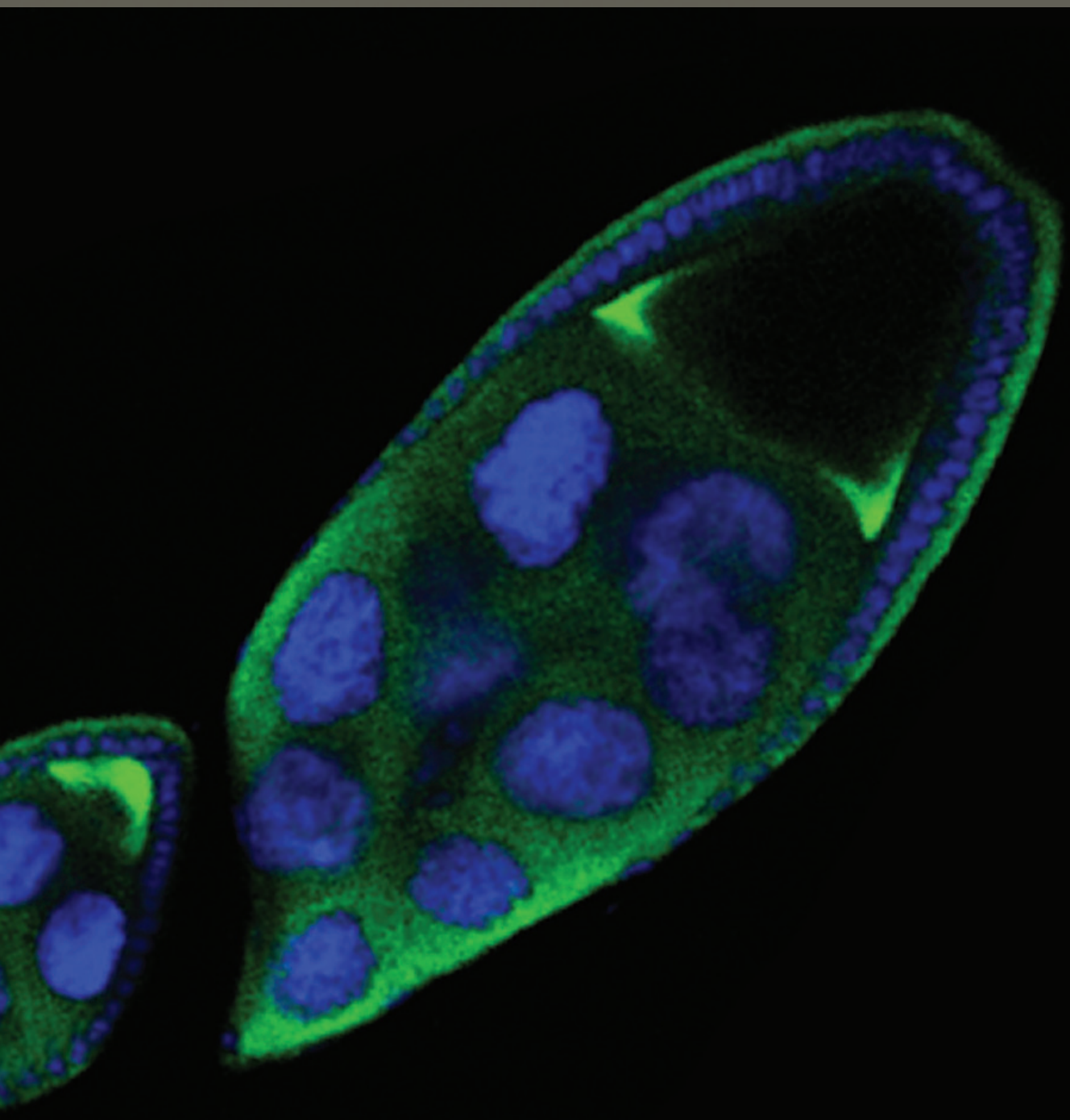
"We're slowly building a picture of what happens when *oligophrenin-1* is perturbed, particularly with respect to various neuropathologies," Van Aelst explains. "This work is some distance from finding a drug target or a therapeutic solution to these problems, but it's the very necessary step that comes after finding genetic mutations that underlie disease."

One experiment

Biological traits that we inherit are usually attributed either to our DNA or molecules that cling to it and modify it epigenetically. Scientists in Prof. Gregory Hannon's lab recently found that the trait of fertility in fruit flies depends on a different factor, which can only be inherited from the mother — a class of small RNA molecules called piRNA.

Julius Brennecke and Colin Malone ran an experiment revealing that piRNAs suppress mobile bits of DNA called *I-element* transposons that disrupt the genome. Because male flies lack piRNAs, progeny that inherit the transposon from their father are sterile. This image by Malone shows 6 sets of developing egg chambers in which each egg is surrounded by blue-colored "nurse" cells. The bright green spots in each egg are fluorescent tags signaling the presence of *I-element* transposons, harbingers of sterility. This result suggests small RNAs may help transmit other important traits, in flies and perhaps other organisms.





For 5 new Ph.D.s, an auspicious beginning

1 Demystifying memory

Allison Blum

American University
Barbara McClintock Fellow,
Entering Class of 2002
Thesis: rutabaga *signaling in distinct circuits supports short- vs. long-term memory in* Drosophila

As a native of Long Island, Blum was always aware of the advantages of spending a few years at CSHL, soaking up the world-class science performed in what is, literally, her own backyard. In Josh Dubnau's lab, she focused on anatomically defining the neural networks involved in memory formation and maintenance, using the fruit fly as an experimental model. She has discovered that short- and long-term memory have their own distinct circuitry and that each can be separately recovered in flies lacking *rutabaga*, a signaling molecule. Blum will soon explore a management track when she begins a job as lab manager of a renowned stem cell and developmental biology research group at NYU.

2 Plant patterns and variations

Daniel Harrison Chitwood

University of California, Davis
George A. and Marjorie H. Anderson Fellow,
Entering Class of 2004
Thesis: *Patterning in leaves via a cascade of small RNAs*

Chitwood's interest in studying the genetics underlying shape formation and organ patterning in plants was initially piqued by a brush with the California wine industry. A scholarship from Gallo Wines and an internship in a grape genetics lab cemented his future plans. Working on his dissertation in Marja Timmermans's lab, he showed that a gradient of small RNAs act as mobile positional signals and instruct growing cells to correctly define the top and bottom layers of leaves — a critical phenomenon called "patterning" that allows a leaf to become optimized for photosynthesis. He now heads back to UC Davis for a postdoc, studying the genetics of natural variation in tomatoes.

3 Untangling brain circuits and signals

Shu-Ling Chiu

National Tsing Hua University
Elisabeth Sloan Livingston Scholar,
Entering Class of 2002
Thesis: *The role of insulin receptor in the development of neuronal structure and function*

The thesis work undertaken by Chiu in mentor Holly Cline's lab addressed a question that has great significance for two major health fields: diabetes and disorders affecting memory and cognition. Although insulin is known to impact brain function, how the signals transmitted by insulin's receptor on nerve cell surfaces influences the establishment and function of brain circuits is a mystery. Chiu showed that insulin receptors regulate the way in which neurons make contact with each other at junctions called synapses and modify the strength with which information is passed from one neuron to the next. She will continue her work as a postdoc at The Johns Hopkins University.

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4 A signaling protein in the brain

Keisha Ann John

University of Maryland, Baltimore
Meyerhoff and Marc U Star Scholar,
Entering Class of 2004
Thesis: *Characterization of the role of DOCK7 in neuronal development*

After finishing a summer internship in neuroscience at WSBS, John stayed on to work on her doctoral thesis with Linda Van Aelst, with whom she discovered a role for the novel signaling protein DOCK7 in neuronal development. John will continue this work as a postdoc at Rockefeller University. Her love for the sciences is rivaled only by her strong belief that all students should be given an opportunity to develop an understanding of the sciences, regardless of their career goals. John eventually hopes to merge her interests in biomedical research and science education policy.

5 A big small-RNA discovery

Jeremy Edward Wilusz

The Johns Hopkins University
Beckman Graduate Student,
Entering Class of 2005
Thesis: *3′ end processing of long nuclear retained non-coding RNAs yields tRNA-like small RNAs*

At the start of his doctoral work in David Spector's lab, Wilusz intended to carve out a research project that would arc away from the RNA-based studies his father, a biologist, had performed. But a single, unexpected band of RNA observed among scores of other bands on a gel and a leap of faith landed Wilusz back in familiar territory – where he discovered an entirely new mechanism by which the cell generates a set of previously unknown small RNA molecules. He heads off to a postdoctoral fellowship at MIT in the laboratory of Nobel laureate Phillip Sharp, an authority on RNA splicing mechanisms.

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3rd Annual Double Helix Medals

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For the third year, Double Helix Medals have been awarded by Cold Spring Harbor Laboratory to extraordinary individuals who have raised awareness of the importance of genetics research. The four recipients, honored at a gala dinner last November, exemplify the Laboratory's aim to highlight the multiplicity of ways in which such efforts can be mobilized "to improve the health of people everywhere."

The dinner held in honor of the awardees raised $3.6 million for CSHL. It will fortify and expand groundbreaking research and education programs, including projects to develop next-generation technologies with which to study the genome.

Two of the awardees are very closely identified in the public mind with efforts to understand the human genome: **James D. Watson, Ph.D.**, and **J. Craig Venter, Ph.D.** Both were honored for their contributions to Scientific Research, specifically, for their advocacy of the public health importance of "personalized genomes." **Sherry Lansing** was honored for Humanitarianism, while **Marilyn Simons, Ph.D.**, and **James Simons, Ph.D.**, were honored for Corporate Leadership.

Dr. Watson and Dr. Venter, both of whom played pivotal roles in the multi-year, multinational effort to sequence the human genome, are among a handful of individuals who have had their entire genome sequenced. The Double Helix Medal commemorates the decision each has made to make his sequence available for scientific use and public viewing on the Internet. Dr. Watson, now Chancellor Emeritus of CSHL, won a Nobel Prize along with Francis Crick in 1962 for their description of the structure of DNA. Dr. Venter, who heads the J. Craig Venter Institute, in addition to playing a critical role in the sequencing of the first-draft human genome in 2001, has led teams that have published the sequences of more than 50 genomes, including those of the fruit fly, mouse and rat.

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Double Helix awardee Sherry Lansing, one of the most powerful executives in Hollywood for almost 25 years, was the first woman to run a major film studio. She is a noted fundraiser for the American Cancer Society, the American Red Cross and her own Sherry Lansing Foundation. She most recently helped to spearhead "Stand Up to Cancer," a nationally televised benefit that aired in September 2008.

Dr. Marilyn Simons and her husband, Dr. James Simons, who runs the private investment firm Renaissance Technologies LLC, are co-founders of the Simons Foundation, a charitable organization founded in 1994 to fund basic research and educational programs in mathematics and the physical and life sciences. With $38 million committed so far, the Simons Foundation expects to provide $100 million in grants in 2009 to autism researchers at more than 30 institutions, including CSHL.

The award dinner was very generously underwritten by Mr. and Mrs. David M. Rubenstein, who were among the Chairs of the event. Others included: The Hon. and Mrs. Alan J. Blinken; Mr. and Mrs. Alan C. Greenberg; Dr. Arthur D. Levinson; Mr. and Mrs. Herbert J. Siegel; and Mr. and Mrs. Erwin P. Staller. The Laboratory thanks each of them and dozens of other dear friends whose support made the evening one to remember.

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1 Fran Biondi and his wife, Trustee Jamie C. Nicholls
2 James D. Watson, Ph.D. and J. Craig Venter, Ph.D.
3 Marilyn Simons, Ph.D. and James Simons, Ph.D.
4 Pres. Bruce Stillman, Ph.D., Sherry Lansing, and Herb Siegel
5 David H. Koch (c), flanked by his wife, Julia Koch (r), and Sherry Lansing

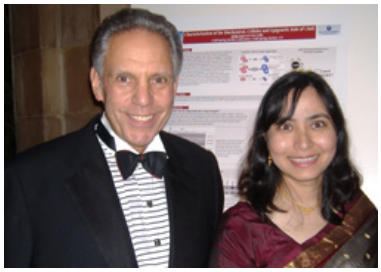
Faculty & Friends

6th Watson School Commencement

Front row (l-r): Dr. Leemor Joshua-Tor, Dean; Allison Blum and Shu-Ling Chiu, Ph.D. recipients; Dr. Jeffrey Miller and Dr. Alfred Goldberg, honorary Doctor of Science degrees. Back row (l-r): Pres. Bruce Stillman; Keisha John, Jeremy Wilusz and Daniel Chitwood, Ph.D. recipients; Dr. Winship Herr, honorary Doctor of Science degree. Not shown: David Micklos, honorary Doctor of Science degree.

CSHL thanks the Montis

A growing partnership between CSHL and the Don Monti Memorial Research Foundation has been significantly strengthened. The Foundation has donated $500,000 to CSHL's cancer genetics research program. "Our relationship with Caroline Monti Saladino and the Foundation has provided us with access to critical technologies that allow CSHL to remain at the leading edge of cancer research," says Professor Scott Lowe, Ph.D., who directs the Tita Monti Cancer Research Laboratory at CSHL. In the picture (l-r): Edward Travaglianti, CSHL Trustee; President Stillman; Dr. Lowe; Caroline Monti Saladino; Richard Monti; Anna Travaglia; Arthur Saladino.



Sass Fellowship in Cancer Research

Martin D. Sass, chairman and Co-Founder of the Sass Foundation, with CSHL's Shilpi Paul, Ph.D., Sass Foundation Postdoctoral Fellow in Cancer Research. Paul, who will receive $75,000 in 2009, is studying the tumor-suppressor gene *CHD5*, discovered by her mentor, Assoc. Prof. Alea Mills, Ph.D., in 2007. Paul received her doctorate from Uniformed Services University of the Health Sciences in Bethesda.

74th Symposium marks Darwin anniversaries

For an updated list of speakers and full Symposium details: http://meetings.cshl.edu/meetings/symp09.shtml

CSH 74th Cold Spring Harbor Symposium on Quantitative Biology

evolution

THE MOLECULAR LANDSCAPE

May 27 – June 1, 2009

Abstract Deadline: March 6, 2009

Organizers

David Stewart, Bruce Stillman and Jan Witkowski
Cold Spring Harbor Laboratory

Topics

Evolution of Molecular Functions
Evolution of Molecular Machines
Origins of Cellular Life
Natural Selection and Speciation
Evolution in Action
Sex and Sexual Selection
Diversity of Life
Genome Evolution
Evolution and Development
Development of Biological Systems
Domestication of Animals and Plants
Human Origins
Evolution of Social Behavior
Evolution and Society
Evolution and the Public

Speakers/Chairs

Leif Andersson, Uppsala University, Sweden
Frances Arnold, California Institute of Technology
Nick Barton, University of Edinburgh, UK
Richard Behringer, M.D. Anderson Cancer Center, Houston
Janet Browne, Harvard University
Carlos Bustamante, Cornell University
Sean Carroll, University of Wisconsin-Madison/HHMI
Thomas Cech, University of Colorado/HHMI
Brian Charlesworth, University of Edinburgh, UK
Quentin Cronk, University of British Columbia, Canada
Jeff Dangl, University of North Carolina
Eric Davidson, California Institute of Technology
Bernard Degnan, University of Queensland, Australia
Daniel Dennett, Tufts University
John Doebley, University of Wisconsin
Russell Doolittle, University of California, San Diego
W. Ford Doolittle, Dalhousie University, Canada
Niall Ferguson, Harvard University
Barbara Forrest, Southeastern Louisiana University
Kevin Foster, Harvard University
Claire Fraser-Liggett, University of Maryland
Seth Grant, Wellcome Trust Sanger Institute, UK
Volker Hartenstein, University of California, Los Angeles
Marc Hauser, Harvard University
David Haussler, University of California, Santa Cruz/HHMI
Paul Hebert, University of Guelph, Canada
Hopi Hoekstra, Harvard University
Gerald Joyce, Scripps Research Institute, La Jolla
Nicole King, University of California, Berkeley
David Kingsley, Stanford University/HHMI
Eugene Koonin, National Library of Medicine, Bethesda
Leonid Kruglyak, Princeton University/HHMI
Richard Lenski, Michigan State University
Michael Levine, University of California, Berkeley
Tom Little, University of Edinburgh, UK
Derek Lovley, University of Massachusetts
Lynn Margulis, University of Massachusetts
Robert Martienssen, Cold Spring Harbor Laboratory
Kenneth Miller, Brown University
Armin Moczek, Indiana University
Eric Olson, UT Southwestern Medical Center
Svante Pääbo, Max-Planck-Institute for Evolutionary Anthropology, Germany
Kevin Padian, University of California, Berkeley
David Page, Whitehead Institute for Biomedical Research/HHMI
Nipam Patel, University of California, Berkeley/HHMI
Steven Pinker, Harvard University
Venki Ramakrishnan, MRC Laboratory of Molecular Biology, UK
Matt Ridley, Newcastle, UK
Gene Robinson, University of Illinois at Urbana-Champaign
Barbara Schaal, Washington University
Eugenie Scott, National Center for Science Education, Oakland
Doug Soltis, University of Florida
Pam Soltis, Florida Museum of Natural History
Jack Szostak, Massachusetts General Hospital/HHMI
Joe Thornton, University of Oregon
Sarah Tishkoff, University of Pennsylvania
Paul Turner, Yale University
Doug Wallace, University of California, Irvine
Tim White, University of California, Berkeley
Edward Wilson, Harvard University
Richard Wrangham, Harvard University

H.M.S. *Beagle* in Murray Narrow, Beagle Channel, Tierra del Fuego.
A watercolor by Conrad Martens, official artist aboard the *Beagle*.
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Celebrating the 200th birthday of Charles Darwin and the 150th anniversary of the publication of *The Origin of the Species*

Registration, abstract submission and further information: http://www.cshl.edu/meetings
e-mail: meetings@cshl.edu · phone: 516.367.8346 · fax: 516.367.8845

Watson on Darwin's achievement

"The achievement of Charles Darwin is that for the first time he put into appropriate perspective man's position on the Earth. By enabling us to see that human beings, like all other forms of life, are the products of evolution, he changed the way we think about ourselves more than any other person who has ever lived, more even than Copernicus or Newton."

— James D. Watson, Ph.D., April 2009

Upcoming public lectures @ Grace Auditorium

2009 Cultural Series

Darwin Commemorative Lecture

7:00 PM
26 May Tue

Sean Carroll, Ph.D.

Remarkable Creatures: Epic Adventures in the Search for the Origins of Species

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7:00 PM
17 September Thu

Rob Martienssen, Ph.D.

Designing Bioenergy Crops: Developmental Problems and Genetic Solutions

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7:00 PM
13 October Tue

Scott Lowe, Ph.D.

Cancer Research at Cold Spring Harbor Laboratory: Our Latest Successes and the Road Ahead

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7:00 PM
22 October Thu

Senthil Muthuswamy, Ph.D.

Breast Cancer Research in 3-D: A New Way of Looking at How Tumors Develop

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**.

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