



Bruce Stillman, Ph.D.

NURTURING YOUNG SCIENTIFIC TALENT IS A defining strength of Cold Spring Harbor Laboratory. The stress we place on investing in the rising generation explains unique aspects of our institution's culture. It likely also helps account for the outsized contribution that the Laboratory has made to modern biology.

The support we provide for young scientists, although both costly and risky, has consistently paid rich dividends. We had a spectacular reminder of this in 2016, a year that marks the 30th anniversary of the Cold Spring Harbor Fellows program.

...young people can explore big questions with a fresh approach, using methods and machines that their predecessors did not possess.

My own experience

When I first arrived at CSHL in 1979, straight from graduate school in Australia, I was thrust into an environment foreign to the way most science is organized today. Then, senior scientists like CSHL Director Jim Watson and Assistant Director Joe Sambrook mentored many early-career scientists, and a select few were granted the freedom to pursue their own ideas and independently publish. Collaborations were encouraged, allowing individuals to achieve more than they might if working on their own.

Jim Watson offered me the opportunity to work on my own independent project, but I also was fortunate to have close mentorship from Mike Mathews, who, like me, was able to pursue his own interests unencumbered with the burdens of seeking research grants. Others, including Mike Botchan, Bob Tjian, David Lane, Ed Harlow, Mike Wigler, Doug Hanahan were granted similar independent opportunities at CSHL after completion of their graduate studies. Each was appointed to Cold Spring Harbor with a conviction that placing bright young people to work on thorny scientific problems in a highly collaborative atmosphere would have the highest impact.

The first Fellows

The CSHL Fellows program was established in 1986 to formalize our ability to attract very talented scientists at the earliest stage of their career. It was modeled after the prestigious Junior Fellows program at Harvard University, but unlike that program, we provided space and substantial funds so that CSHL Fellows could pursue experimental research. In 1986 Richard Roberts, then a senior faculty member, and Jim Watson succeeded in recruiting a gifted young scientist from Harvard named Adrian Krainer.

The very first CSHL Fellow, Adrian had just completed his doctorate under the mentorship of Harvard's Tom Maniatis, a former member of CSHL's faculty and then a member of the CSHL Board of Trustees. In 1986, Krainer could have pursued a conventional postdoctoral research position within a lab at any number of first-rank institutions. Instead he came to CSHL because of the freedom that the Fellows program offered, backed up by the nurturing of Rich Roberts, a highly successful scientist who contributed amazing discoveries in the field Adrian was entering.

Forty years ago, Roberts, Louise Chow and Phillip Sharp were the first to notice "split genes"—a phenomenon that we now refer to as RNA splicing. Although Roberts, Chow and Sharp had come to Cold Spring Harbor at the beginning of their own independent careers in the early 1970s to study tumor viruses, Roberts, Chow and colleagues at Cold Spring Harbor, and separately Sharp who moved to MIT, discovered a phenomenon that transcended the cancer research in which they were engaged. Their research revealed that RNA messages copied from the genetic code in DNA are edited, or spliced, before the resulting messenger RNAs (mRNAs) are translated

into proteins. This discovery, recognized with a Nobel Prize in Physiology or Medicine to Roberts and Sharp in 1993, revolutionized our understanding of how genes are organized in our genome and how they evolved.

Adrian Krainer

As the first CSHL Fellow, Adrian worked on perfecting a method, called a cell-free system, that he had developed

in his graduate work to investigate the cellular machinery involved in messenger RNA splicing. Here Adrian was given a wide berth to follow a subject that he was passionate about. He seized the opportunity and began the painstaking process of isolating different components of the splicing machinery. He was not alone in this branch of research, but from the outset it was clear to me that he would become a leader.



This is Emma Larson, now a spunky and mobile three-year-old, thanks to a drug developed from CSHL research. Barely able to hold her own bottle as a one-year-old, Emma was diagnosed at 13 months with type 2 spinal muscular atrophy—a theretofore untreatable, deadly disease. On her second birthday she was old enough to be enrolled in a clinical trial for the drug now called Spinraza™. At that point, Emma was no longer able to sit up. But as the drug began to work its scientific miracle, she progressed from crawling to walking with crutches by the time she entered preschool. Emma and her family visited Adrian Krainer's lab this year to share her continuing progress and delightful smile.

The Laboratory's investment in Adrian has been repaid in many ways over 30 years, but in 2016 both he and the Laboratory had the special satisfaction of seeing basic-science discoveries made in his lab come to fruition in the form of a drug that remedies a deadly neuromuscular disease of childhood called spinal muscular atrophy, or SMA.








The day before Christmas of 2016, this drug, first identified by Krainer's team as ASO 10-27 and later developed and commercialized by Ionis Pharmaceuticals and Biogen as Spinraza™, was approved by the FDA for use in SMA patients.

Compensating for a genetic defect that reduces the amount of a particular protein in neurons that innervate muscles, the drug is already saving lives. It is a great example of why not only the Laboratory, but the government of the United States, make significant investments in basic research.

Each CSHL Fellow is appointed for three years with full financial support from CSHL. Afterward, they can move up our academic ranks or transition to another institution. The CSHL Fellows program has launched many fine careers.

Carol Greider

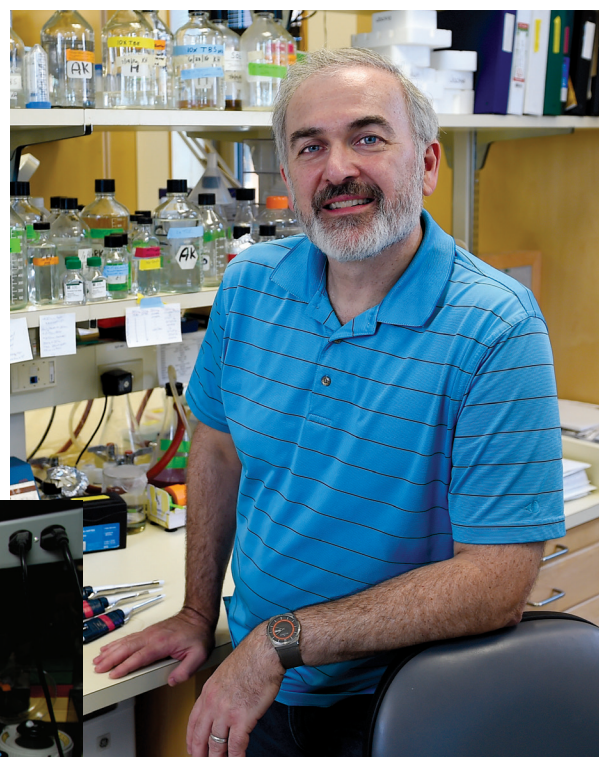
Carol Greider, our second CSHL Fellow, began her independent career here in 1988, making discoveries about the structure of the enzyme that maintains telomeres, the ends of our chromosomes. These

1986	1988	1989	1991	1994	1995
Adrian Krainer Professor	Carol Greider Professor & Director	Eric Richards Professor & V.P. for Research	David Barford Group Leader	Ueli Grossniklaus Laboratory Head (PI)	Scott Lowe HHMI Investigator, Chairman & Member, Professor
 Cold Spring Harbor Laboratory	 JOHNS HOPKINS SCHOOL of MEDICINE	 BTI BOYCE THOMPSON INSTITUTE	 MRC Laboratory of Molecular Biology	 University of Zurich	 Memorial Sloan Kettering Cancer Center  Weill Cornell Medicine Graduate School of Medical Sciences

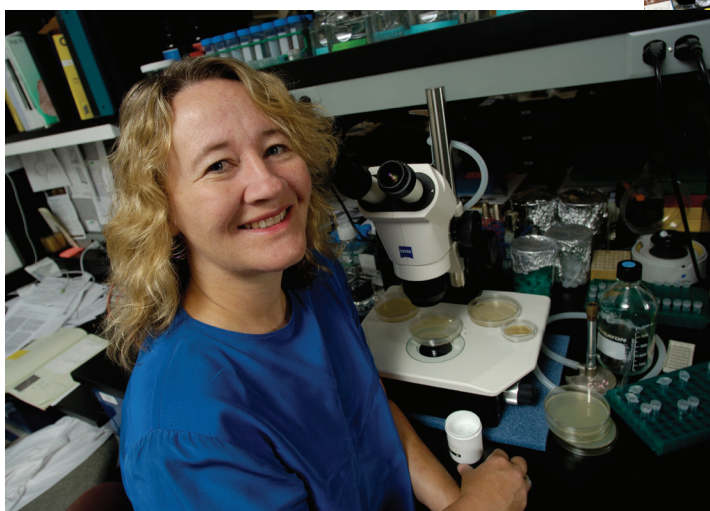
independent studies, along with her pioneering graduate studies at the University of California, Berkeley, were integral in the body of work recognized by her sharing the 2009 Nobel Prize in Physiology or Medicine. See the timeline above, highlighting all previous CSHL Fellows and their current appointments.

A youth culture

There is an old expression that “youth is wasted on the young.” Nothing could be further from the truth in science, which relies upon the young to move entire fields forward. It may sound paradoxical, but one of the strongest reasons for investing in young scientists has to do



Adrian Krainer, the first CSHL Fellow, became a Professor here in 1994. His laboratory has been dedicated to understanding a fundamental biological process about how genes are expressed in cells. This research and Adrian's innovation developed a drug that is now saving children like Emma, who is pictured on the previous page.



Carol Greider, an early CSHL Fellow, became an assistant investigator and then an Investigator here before moving her laboratory to the Johns Hopkins University School of Medicine. There, she is currently the Daniel Nathans Professor; Director, Molecular Biology and Genetics; and Bloomberg Distinguished Professor of Biology.

with what they don't know. I have come to appreciate this during my many years as president. Young people come into science with enthusiasm, with fresh ideas and the willingness to work hard. The very best of them are not burdened with current dogma.

An advantage of what I call the “naiveté of youth” is that they can pose important questions—some that may well have been asked by investigators of prior generations, but they do so unencumbered with accumulated bias that often slows the progress of more senior scientists. Due to the continual march of technology, young people can explore big questions with a fresh approach, using methods and machines that their predecessors did not possess. This story is repeated,

1998	2000	2000	2004	2004	2008	2008
Marja Timmermans Professor	Terence Strick Professor	Lee Henry Research Specialist	Ira Hall Associate Professor & Associate Director	Patrick Paddison Associate Member	Florin Albeanu Associate Professor	Christopher Vakoc Associate Professor
						

over and over. Our young people are right now making discoveries and developing new technologies that will inform their science and empower the generation that follows them.

A startup package today typically includes a guarantee by the Lab to cover up to \$2.5 million in direct costs for the incoming faculty member, and with all factors included involves an expenditure of some \$4 million over 5 years. That's a substantial commitment, but one we are happy to make because we want to see people succeed. During the initial 5-year period, we expect a junior faculty member to secure grants from government and private funders sufficient to support their independence. At the same time, we are deeply committed to supporting innovative aspects of their research, by connecting them with philanthropic supporters or funding from our endowment.

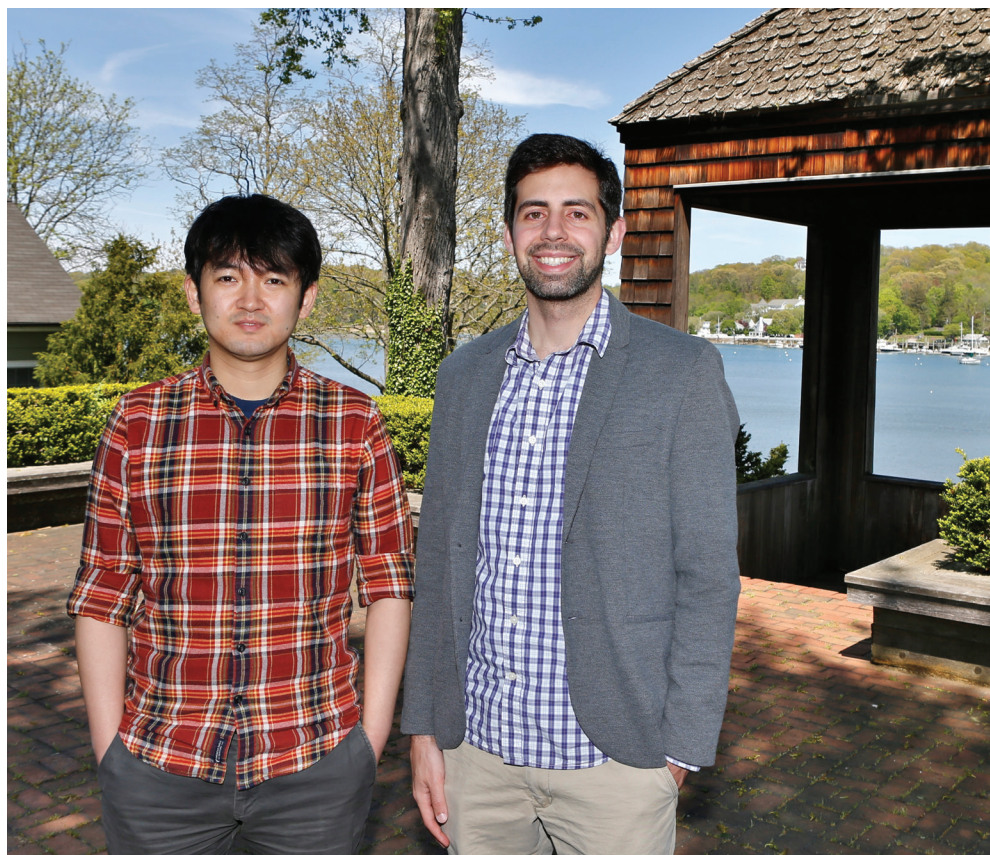
CSHL has a youth culture. While we depend upon senior faculty to mentor and guide the careers of our junior faculty, the ratio of senior to junior members is roughly 2 to 3. At peer institutions the ratio is weighted heavily in the opposite direction: at Rockefeller University and the Salk Institute, for instance, there are 7 or more senior faculty for every 2 or 3 junior faculty. Ours is a culture that bets on early-career scientists; our peers reward past achievement.

The same can be said of the grant culture at the National Institutes of Health. On average, a scientist receiving a first-time research (R01) grant does not receive it until age 42. The prerequisite is that the grantee is expected to have preliminary results; the NIH

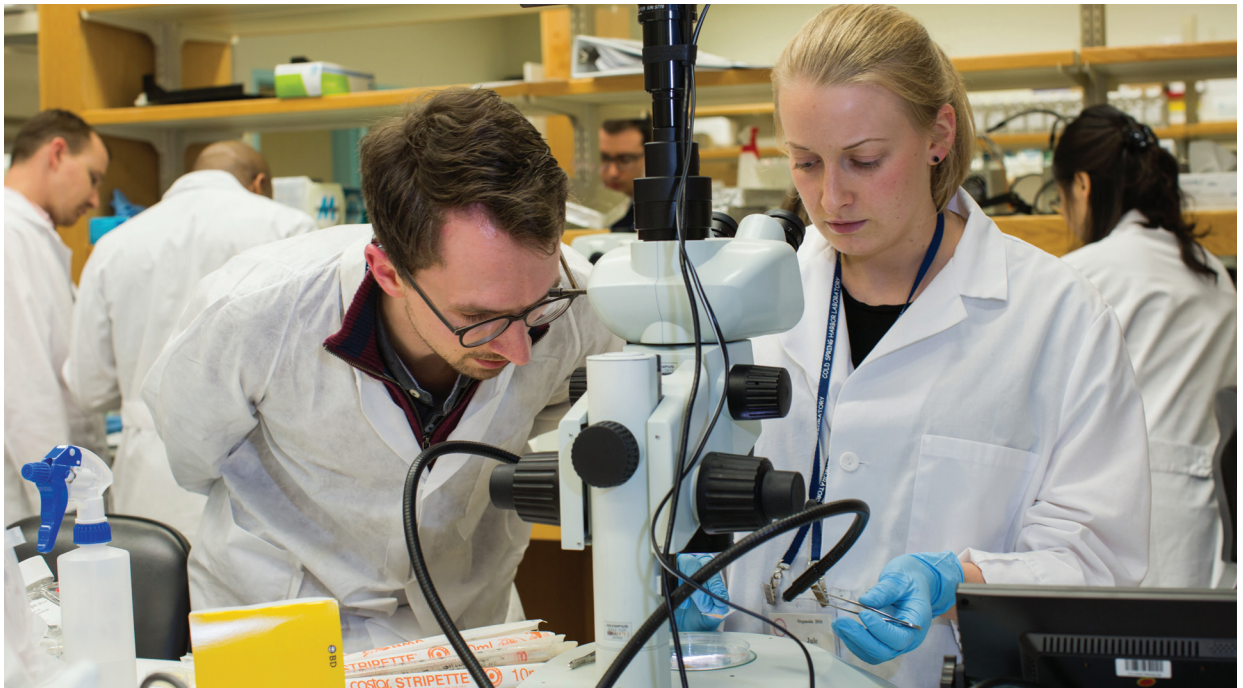
does not, presently, support people, but rather supports projects. This is not the case at CSHL, where we give the brightest young people a chance to become successful. That we often succeed is measured in the rapidity with which we promote junior faculty, compared with the much slower rate at universities.

A community of science

The Laboratory as a community of science is one of the strongest factors in our ability to perennially draw the best young talent here. Our Meetings & Courses Program



Current CSHL Fellows: Lingbo Zhang has a Ph.D. jointly from the Massachusetts Institute of Technology (MIT) and the National University of Singapore; and Jason Sheltzer has a Ph.D. from MIT.



At CSHL, young investigators have easy access to the latest technologies through the CSHL Meetings & Courses Program and dedicated institutional shared resources.

brings about 10,000 members of the biology community to our campus every year. This places everyone on our faculty and scientific staff right at the confluence of the many great rivers of information flowing into our field. My own exposure to the CSHL yeast course changed the direction of my career, and there are many other similar stories. Cold Spring Harbor is a place where you can branch out, change focus, add new areas of expertise to the one you were initially recognized for. This is part of what it means to have a youth culture.

Our institution also has remarkable state-of-the-art shared research resources, which enable faculty, students and postdocs to use the most sophisticated apparatus and techniques. Such experimental resources not only promote collaboration, but also allow small groups access to technologies that would be difficult to establish in their own lab. This is in part why a CSHL Fellow can be successful.

For all of its virtues, this is an expensive proposition that carries a fair amount of risk. When we invest in a smart young person, we can never be certain of his or her success, and know that he or she may leave us, to be replaced by another young person of talent and promise. This movement keeps us on the leading edge, but means we must keep investing in people, at costs that have soared over the last decade. Our Fellows program is supported only by our annual fundraising, and to sustain it over the long run, we need substantial endowment funds to provide a constant level of support.

A model for others

Judging from our successful Fellows program and the similar Fellows Program at the Whitehead Institute at MIT, investment in early career independence can lead to great science. I suggest that more institutions establish formal programs that allow for this opportunity. The NIH has introduced a funding mechanism to support early-career scientists straight out of graduate school, but it suffers because these fellows must first be appointed to a position at a university or research institute. Many universities do not have an organized environment to nurture a fellows program.

Mentoring is critical for an early career independent researcher to succeed, as is access to shared research resources. But even before that, there needs to be a strong institutional commitment that encourages the best graduate students to pursue an independent career rather than continuing training with a senior scientist. While these positions are not for everyone, for the right person immediate independence can be liberating and lead to great scientific achievements. Our nation should explore more opportunities for such talented people.

Bruce Stillman

April 2017