HHMI’s new chief scientific officer Erin O’Shea applies an uncommon intensity to her research and training—of students and German shepherds.

By Sarah Goforth
Photography by Kathleen Dooher
Erin O’Shea does not waste time. She finished a Ph.D. in two and a half years, rose from novice to world champion dog trainer in under three, and, at age 47, is moving into an executive leadership role at HHMI.

The eldest of five children, O’Shea is just six years older than her youngest sibling Meggan. Both women describe their middle class upbringing in western New York as happy and ordinary. Their father ran a residential contracting business, and their mother left a career in physical therapy to run the household. All the O’Shea kids performed well in school and excelled as athletes.

But there was something different about Erin. “She was intensely focused, much more so than the rest of us,” says Meggan O’Shea. “With Erin it’s always been, she’s going to do what she wants to do, she’ll do it very, very well, and she’ll do it fast.”

Andrew Murray, a longtime colleague of O’Shea’s, puts it another way: “Soon after people meet Erin, if you were to ask them how fast this woman could gnaw through a quarter-inch bar of steel, they’d be like, ‘oh, probably 90 seconds.’” After hearing O’Shea present her research as a graduate student, Murray was so impressed he helped recruit her to the University of California, San Francisco (UCSF), and later to Harvard University, where she’s been since 2005.

O’Shea, an HHMI investigator since 2000, maintains a prolific research lab focused on understanding how cells sense and respond to their environment. Her contributions range from discovering how single cells adapt at the molecular level to changing levels of light and stress to analyzing randomness in gene expression patterns. Her work has advanced the broad understanding of basic biological mechanisms and helped scientists studying cell growth patterns in cancer and other diseases.

In July, O’Shea will become vice president and chief scientific officer at HHMI, moving with her husband Douglas Jeffery to Chevy Chase, Maryland, where HHMI is headquartered. She views the job as both an opportunity to do something new and as a natural extension of her past work—as a scientist, administrator, mentor, and educator.

Influencing Undergrads
By the time O’Shea joined Harvard, she felt an obligation to give back to the scientific community by training and educating the next generation of researchers. As director of Harvard’s Faculty of Arts and Sciences (FAS) Center for Systems Biology, O’Shea has recruited and mentored many junior faculty. With a tight-knit group of colleagues, she created an innovative undergraduate science course.

“A lot of people with her level of accomplishment are not great listeners, but she’s interested in people and makes time for them,” says Dan Kahne, a Harvard chemistry professor who created the course Life Sciences 1A with O’Shea and four other faculty members. “With students, that’s very important. It doesn’t have to be all about her.”

The enormously popular course is a matter of pride for Kahne, O’Shea, and the others on the faculty team. They present science as a detective story at the intersection of chemistry and biology—the two disciplines that drive progress in the life sciences today. Students explore a handful of experimental case studies rather than a body of facts and prefabricated lab exercises. The course draws more than 500 students a year, and O’Shea reports that the number of life science majors at Harvard has grown by 40 percent since its inception.

“We choose topics that capture students’ interest and motivate them to learn the underlying detail,” she says. “We tell them like mystery novels with a thread that hooks them all together.” O’Shea keeps regular office hours for her undergraduate students, meeting with them one on one and often helping them find research positions in labs.

“I came to Harvard in part because I wanted to teach undergraduates, because the people who taught me at that stage of my education had a big influence on my career,” she says.

Sparks of Interest
As a high school student in Leroy, New York, O’Shea enjoyed learning about science but envisioned herself as a veterinarian or doctor. It wasn’t until her sophomore year at Smith College in Northampton, Massachusetts, that she learned what it meant to do science. She began conducting research on catalysts in an inorganic chemistry lab and was allured by firsthand discovery.

“I was excited to be doing something where, unlike the science course labs I’d had before, we didn’t know the answer. We were actually finding the answer,” she says.

Her famous focus kicked in. “There was a pretty marked change in her,” says her sister Meggan. “She had found something that she loved and put all her energy into it. By the second
part of her sophomore year, she was around a lot less. We all noticed it, that she was really dedicated to what she was doing.”

By the time Meggan entered Smith in 1989, her sister had published a groundbreaking paper as a graduate student in Peter Kim’s lab at the Massachusetts Institute of Technology (MIT). It had people talking. “My bio professor said to me, ‘Are you one of the O’Shea’s?’ and I knew she was taking off,” recalls Meggan.

Driven by Questions
Erin O’Shea distinctly remembers the moment that fueled her running start. In the latter part of her senior year at Smith she began working at MIT’s Whitehead Institute for Biomedical Research. One afternoon the following summer, she was reading the journal Science at a picnic table outside the Whitehead, where she had taken on a short-term research project on nucleic acids in Kim’s lab. A paper by Steve McKnight, a biochemist now at the University of Texas Southwestern Medical Center, described a protein motif called the leucine zipper—a key part of many transcription factors that guide cells to turn genes on and off.

“I had this idea that McKnight’s model was basically correct but wrong in detail,” she remembers. O’Shea had taken a course at Smith that focused on a class of structural proteins called coiled coils, and she thought she recognized their hallmarks in McKnight’s protein motif.

So she went to Kim, who had worked on protein folding, and he let her try to make the peptide and see if it was a coiled coil. “And it was. It was a big result in the field of protein folding, and it was an idea I had come up with. It was very exciting.” O’Shea’s work changed the way the scientific community understood the leucine zipper and, by extension, how transcription factors interact with genes.

To her parents’ dismay, O’Shea decided not to enter the M.D., Ph.D. program at Yale. She had no alternative long-term plan. Instead, she stayed at MIT to follow the leucine zipper trail in Kim’s lab. “It wasn’t some big vision I had about how it would help my career. It was more, I want to do these experiments, and I have to stay here if I want to do them.” The following January, she was admitted to MIT’s Ph.D. program, funded by an HHMI predoctoral fellowship.

She solved the crystal structure of a leucine zipper in fine detail two years later, a paper that caught the attention of Francis Crick, famed for his discovery with James Watson of the DNA double helix. Crick had proposed the structure of a coiled coil in the 1950s. He wrote the young O’Shea a letter, congratulating her on the high-resolution structure. Her confidence boosted, O’Shea presented her work in a seminar at UCSF the following year.

Andrew Murray was a junior faculty member at UCSF at the time. “I went home and told my wife I’d seen the best seminar I’d ever heard, and it was given by a graduate student who looks like she’s fresh out of college,” he recalls. “It was a combination of the quality of the work, the way she framed it conceptually, and the confidence and panache with which it was presented.”

UCSF offered O’Shea a faculty position—a rare opportunity...
for a scientist just out of graduate school—and gave her two years to do whatever she wanted. She split the time working with HHMI President Robert Tjian, who at the time was a Hughes investigator at the University California, Berkeley, and with Ira Herskowitz at UCSF.

In Tjian’s laboratory, O’Shea became interested in how gene expression is regulated by chromatin—the tight packages of DNA and proteins inside the nuclei of cells. It was a divergence from her protein structure work. “Tjian was incredibly supportive, even though I was heading in this new direction,” she says. “He wanted my curiosity to guide what I did, rather than telling me what approach to take.”

At that time, much of the transcription field was focused on studying transcription in test tubes, says O’Shea. She wanted to examine the system in a physiological context, inside the chromatin. That decision led her to the Herskowitz lab, where researchers were studying transcription factors in yeast. Herskowitz had determined the genetic pathways that allow yeast to reproduce, and he supported O’Shea’s decision to refocus on biology. “I was used to doing physical chemistry, so it was another big change in my career track,” she says.

Expert Timekeeping
That change stuck. At Harvard, O’Shea’s lab of 15 students and postdocs, which occupies a modest space on the second floor of the FAS Center for Systems Biology, is surprisingly diverse for its size. Lab members represent half a dozen countries and just as many disciplines, and they study biology at the cellular level in mice, yeast, and bacteria. No question is off-limits as long as it is both interesting and important, says O’Shea, but the lab’s primary areas are still gene expression and regulation—how cells turn genes on and off or dial them up and down. In recent years O’Shea has also taken an interest in the molecular clocks that govern circadian rhythms—the 24-hour patterns of activity that help organisms predict the availability of and respond to warmth, light, and nutrients.

“There’s something special about the clock in the cyanobacterium,” says O’Shea, referring to the blue-green algae that are responsible for 70 percent of all photosynthesis on Earth. The molecular clocks inside cyanobacteria anticipate daylight and then drive the production of proteins needed for photosynthesis. “There was this remarkable paper where a Japanese team [led by Takao Kondo] showed they could take the three proteins that make up the clock, mix them together in a test tube, and reconstitute oscillations with 24-hour periodicity,” O’Shea says. In other words, the clock proteins appeared to be sufficient to keep time, independent of any other processes of the cell. This was contrary to conventional wisdom, which held that circadian clocks are governed by cycles of transcription and translation in a cell—in which a gene produces a protein that performs a task and then eventually halts its own production. When O’Shea read the paper, she couldn’t resist asking: how do these proteins function absent those cellular cues?

“People thought the clocks in all organisms had a common architecture that relied on this transcription–translation feedback,” she explains. Instead, the clock appeared to rely on biochemical interactions of the three proteins. To stay synchronized for weeks at a time, it needed only to be supplied with the energy-storing molecule adenosine triphosphate (ATP).

Kondo’s team had wowed the biochemistry community with this news, but the mechanism by which these three proteins kept ticking remained a mystery. Intrigued, O’Shea tested the proteins in different conditions and eventually described the process by which it happened—phosphate groups from the ATP being the key ingredient—in a detailed mathematical model.

The Meaning of Mentorship
The cyanobacterial circadian clock is a small but illustrative piece of O’Shea’s research portfolio. She encourages the researchers in her group to follow their interests and develop questions independently, even if they diverge somewhat from her own. Two of her postdocs, for example, are testing drug-screening platforms, projects that are more clinical than O’Shea might choose out of a more fundamental

O’Shea described the process by which three proteins in cyanobacteria, like the ones shown here, synchronize the organisms’ circadian clocks so that photosynthesis occurs during daylight hours.
I was Googling the word ‘Schutzhund,’ and the next thing I knew I was spending three months in Germany with Zambo, preparing for the world championship,” she says. It paid off. Zambo earned the world championship title in 2011. At age 3, he was the youngest winner ever, an early achiever like his owner. Rumors of a fluke victory circulated, but Zambo won again the following year. After that high point, O’Shea decided it was time for him to retire: “Like Michael Jordan, you gotta go out on top,” she laughs.

That’s just what Erin does,” says HHMI professor Richard Losick, another Harvard colleague. “She picks something up, because it’s important or because it interests her, and before you know it, in the blink of an eye, she’s the best in the world.”

The Leadership Stamp

“Erin is one of those people who have leadership stamped on their foreheads,” says her friend and colleague Andrew Murray. “Sometimes when she’s running at full intensity, it is easy to mistake her for one of those people who is occasionally wrong but never in doubt. But she has the intelligence, courage, and grace to go back and reflect, and if necessary, rethink her position. She has great judgment as an administrator.”

In her new role as vice president and chief scientific officer at HHMI, O’Shea will lead the Institute’s flagship Investigator program and its many extensions. She will maintain her Harvard lab, Skypeing in for lab meetings and returning in person every month.

As at Harvard, O’Shea sees her most important job at HHMI as finding, recruiting, and supporting the best people. “If you want people to succeed, you’ve got to pick the people well and do everything you can to support them,” she says.

For O’Shea, offering support often means yielding control, says her colleague Dan Kahne, citing an analogy from a shared trip to the O’Shea family’s lakeside cabin in New Hampshire. Kahne recalls: “My wife and I weren’t sure about bringing our kids, but Erin said, ‘Are you kidding? Pack up the water skis and bring everyone.’ She was the only one who would let my son take the canoe out by himself. I told her that was a good way to lose a canoe. She said, ‘But look how much fun he’s having. It’s the only way he’ll learn.’”

Giving scientists freedom—to explore untested ideas; to pursue unexpected leads; to enter, and even forge, new disciplines—is a cornerstone of the HHMI model. As Kahne sees it, there is no one better suited to deliver on that promise than O’Shea.