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By Karen Hopkin

Cool Cloning

Lynn Cooley figured she'd study sea creatures, then decided to revolutionize *Drosophila* genetics instead.

Lynn Cooley grew up wanting to be a marine biologist. "I thought it would be fun to study sea creatures," she says. So Cooley enrolled as a zoology major at Connecticut College in New London, and then took a semester off to volunteer on a research cruise conducted by the Woods Hole Oceanographic Institute. "I thought, this is fantastic, I'm going to get on this ship and find out how much I love marine biology," she says. The voyage dredged up samples and took photographs of the ocean floor from San Juan to Woods Hole, and Cooley had a great time developing photos, repairing nets, and helping catalog what the crew found. "But I decided I really didn't like marine biology very much at all."



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What happened? "The taxonomy was a little tedious," says Cooley. "Scraping up a few animals off the ocean floor and trying to figure out what they are and what their population density is. ... I don't know. I think I'm just more attracted to an experimental approach to science."

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The following summer, she took her first laboratory course at the Woods Hole Marine Biological Laboratory. "I was thrilled to get into a biochemistry lab where I could actually do experiments: I got to isolate proteins and figure out how they work best." Best of all, she was near the beach. "You could go swimming while your reactions were running," she says. "So maybe that was marine biology."

"I'll bet when she was at the bench full-time, her experiments always worked. A few people have that kind of gift at the bench. She's one of them." - Douglas Robinson

Now a faculty member at Yale, Cooley does her dredging in the *Drosophila* genome and has come up with a handful of genes that are key to oocyte development-work that Howard Hughes Medical Institute investigator Allan Spradling, of the Carnegie Institution, hails as pioneering research in the cell biology of development. But Cooley's real claim to fame came from work

she did as a postdoc in the Spradling lab in the late 1980's. There she helped to develop the technique of transposon-insertion mutagenesis, which has revolutionized *Drosophila* genetics. "This became the most common way that people cloned genes," says Spradling.

To Make an Omelette...

In 1976, inspired by her experience at the bench, Cooley entered the graduate program at the University of Texas in Austin. "But the program I was in there wasn't quite the right fit for me," she says. "So I decided to write my master's thesis, leave the program, and work as a lab tech for awhile."

Homesick for Connecticut, Cooley headed to Yale, where she worked in the laboratory of Dieter Söll. After a few months, "Dieter brought me into his office and asked me what I was going to do with my life. I didn't know, so he proceeded to tell me I was going to finish my PhD by doing my research in his lab."

"I felt that's what her future should be, something other than being a technician," says Söll. "She was very original, very independent-thinking, and she showed a lot of promise. And she has certainly fulfilled that promise."

When Cooley was just starting out, most investigators were using chemical

mutagenesis to produce interesting phenotypes, but finding the responsible gene was sometimes an insurmountable challenge. "So the promise of cloning and recombinant DNA was still just a promise," says Spradling. "Unless you could associate a mutant phenotype with a specific protein-coding sequence, you couldn't do all the cool stuff we like to do today."

"Sitting here in 2008, it's hard to remember that up until the late 1980s, identifying mutant genes was not trivial," says Douglas Robinson of the Johns Hopkins University School of Medicine, and one of Cooley's early graduate students. Spradling agrees. "It was not uncommon for a person to spend three years as a postdoc trying to clone a gene and still not get it. We knew people in that situation." But transposon mutagenesis changed all that. If Spradling and company happened to hit one of their colleagues' target genes with a P-element transposon, he says, "we'd send them the strain. And they'd have their gene in a day."

The approach works so quickly because the insertion of the transposon in or near the gene leaves a traceable tag. "You do your mutagenesis, screen for a phenotype you like, and then clone the DNA flanking the P element," says Cooley. The resulting first-author *Science* paper, published in 1988, "put Lynn on the map," says Esther Verheyen of Simon Fraser University in British Columbia, another of Cooley's first graduate students.

Cooley was originally drawn to Spradling's lab because of his focus on oogenesis. "It's got to be one of the most fundamentally interesting processes in biology," says Spradling. "The oocyte is the only cell that can develop into a multicellular animal. But we don't really understand why." Her first P-element screen generated mutants that were defective in their ability to produce eggs.

So when Cooley established her own lab at Yale in 1989, she set out to characterize these mutants. In *Drosophila*, oocytes develop in a structure called an egg chamber, which Cooley describes as "a package of cells devoted to making one egg." Included in that package are 15 nurse cells, each of which is attached to the oocyte by a thin bridge of cytoplasm, like a balloon squeezed down the middle to form two connected spheres. The nurse cells support the growth of the oocyte, eventually emptying their entire contents - cytoplasm, ribosomes, mitochondria, essentially everything except their nuclei - into the developing egg.

At least that's what normally happens. In two of Cooley's mutants, the nurse cells never managed to complete the transfer. As a result, Cooley says, "the eggs made by these females were about half the size they should be. And the females were completely sterile." Cooley decided to figure out why.

The first gene she cloned encodes an actin-binding protein called profilin. And she showed "with very beautiful microscopy and eventually molecular analyses, that it participates in oogenesis by a mechanism that no one would have

predicted," says Dennis McKearin of the University of Texas Southwestern Medical Center, another former Spradling postdoc. Profilin, along with fascin and villin - proteins whose genes Cooley later cloned - crosslink the actin bundles that anchor the nurse-cell nucleus in place. Without these accessory proteins, the nurse-cell nuclei jam the opening between nurse cell and egg such that no more cytoplasm can cross. That work appeared in *Cell* in 1992.

"Her experiments always worked"

In the meantime, Cooley cloned a second gene that, when mutated, also produces sterile females that make pint-sized eggs. This one, called kelch, encodes a protein whose sequence didn't at first give any clues to its function, so Cooley hoped that an antibody would indicate what it might do. "Sometimes you're lucky, sometimes you're not. With kelch we were fantastically lucky," she says. "The antibody localized almost specifically to ring canals," the actin-rich structures that hold open the cytoplasmic tunnels between nurse cells and their egg.

"It was a stunning localization pattern," notes Robinson, and it focused Cooley's attention on what might be wrong with ring canals in kelch mutants. "It became very clear, very rapidly, that the actin filaments were completely disorganized in kelch mutants," she says. As a result, the opening between the cells was too small to allow the cytoplasm and organelles to flow through. Those findings appeared in *Cell* in 1993.

"When Lynn first started at Yale, we had one *Cell* paper after another," says Verheyen. "They were really comprehensive analyses based on the techniques that were available at the time. Lynn is really thoughtful, really meticulous. When she publishes something, people trust the results and know the work has been done really rigorously."

Denise Montell of the Johns Hopkins School of Medicine, another Spradling trainee, agrees. "Her work serves as a model for how to do these studies," she says. "It's always carefully and beautifully done and it holds up in the long run. So if Lynn says something is true, you can take it to the bank."

She's also a crack molecular biologist, says Robinson. "I'll bet when she was at the bench full-time, her experiments always worked. A few people have that kind of gift at the bench. She's one of them. She can do an experiment and get the answer. I think Lynn is probably sort of supernatural in those regards."

And the answers she's found are not only relevant to *Drosophila* eggs; the same structures are found in the germline cells of almost all animals. "It's kind of neat to see how this little cell in fly ovary turns out to have implications for how mammalian oocytes develop," says Robinson.

"She took a relatively obscure biological phenomenon - the maintenance of these connections between cells - and, using a lovely combination of forward genetics followed by beautiful cell biology and biochemistry, has turned it into something of much wider interest. It's really textbook material," says Yale's Thomas Pollard.

Gotta Jet

In addition to continuing to explore exactly how these and other proteins she's discovered help build a healthy egg, Cooley has recently adapted her transposon technology to tag *Drosophila* proteins with green fluorescent protein (GFP). "We've produced thousands of lines of fruit flies that each make a GFP fusion to a different protein," she says. The work should help her localize proteins of interest to her lab and to the entire fruit fly community. "She's just always been one to seek to develop new technologies that will contribute to accelerating progress in the field," says McKearin.

That same dedication to the scientific enterprise also motivates her management of the biological sciences graduate programs at Yale. "It's a huge job, an important job, which she does beautifully and diplomatically," says Pollard. Training the next generation of scientists in her lab and in the school, adds McKearin, "is just an important part of who she is."

Doing all that, while raising her two daughters, leaves her no time for the hobby she took up as a young assistant professor: flying. "I was getting up, going to work, working late, every day. I decided I was getting boring," says Cooley. "So I needed a hobby. But it had to be a pretty good hobby. Otherwise, I would just stay in the lab." So she learned how to fly a plane, an experience that - compared to running a lab, managing a handful of Yale's graduate programs, and being a mom - she finds relaxing. "It takes all your mental energy to focus on what you're doing, which lets you leave behind all the other balls you're trying to keep in the air," says Cooley. "Plus it's peaceful, flying above 'life as usual.'"