Coleen Murphy: How to stay young at heart, body, and mind

Murphy studies reproductive and cognitive aging in *C. elegans*.

When Coleen Murphy was growing up in Kansas, her parents subscribed to a magazine on California living. Murphy remembers flipping through magazine pages filled with lush photographs of California scenery and cuisine. Perhaps that's why she felt so at home when she arrived in California for graduate school at Stanford (1).

Later, during her postdoc with UC San Francisco's Cynthia Kenyon, Murphy also moved into her scientific home: studying the aging process using *C. elegans* (2). Since then, from her own lab at Princeton University, Murphy has continued to open new doors onto the aging process, showing how to extend reproductive lifespan (3, 4) and how learning and memory are affected in animals whose lifespan has been extended through experimental interventions (5). We called her to hear more about how her work is maturing.

YOUNG SCIENTIST

What did you want to be when you were growing up?

The funny thing is I always thought I would be a professor in a college town. I don't know where I got that idea, because my family didn't live in a college town and I'd never been to one. My parents had moved us from Mountain View, California, to a pretty rural part of Kansas when I was four, and the schools there didn't really have the facilities to focus on science education. But I had an English teacher, Cynthia Jarrold, who decided I should take the SAT and who drove me 45 minutes to the place they were giving the test. From that I won a National Merit Scholarship and then wound up at the University of Houston, which was giving out full scholarships to National Merit Scholars.

> "I decided I wanted to study a bigger, more wide-open question."

When did your interest in biology begin?

In college I started out in chemical engineering because, when you're in high school and you do well in science and math, people tell you that you should be an engineer. But then I started taking science courses, and I realized I really liked the questions in biology. When I switched into biophysics and biochemistry, which is what I ended up graduating in, it was really eye-opening to read the primary literature and see that, wow, I could do something like this myself. I could discover something new.

As a graduate student, you studied myosin…

When I interviewed for graduate school at Stanford, one of the people I spoke with was Jim Spudich. Jim loves talking about myosin, and his enthusiasm is infectious. I really got excited about working with him for that reason, and I think it was the right choice. The one mistake I made in graduate school is that I didn't talk with Jim enough about my work. I now realize that I should've done more of that, because he's a fun guy to talk to. [Laughs]

AGE-OLD PROBLEM

Why did you switch fields so dramatically as a postdoc?

Before my graduate studies on myosin, I'd done protein crystallization in Johann Deisenhofer's lab at UT Southwestern, and in Jim's lab I worked on myosin structure/function. I had very intensively studied single proteins, and I decided I wanted to study a bigger, more wide-open question. Towards the end of grad school, I heard Cynthia Kenyon speak, and I thought she would be someone who would be fantastic to work for, because she's a really creative thinker. One of my classmates, Joe DeRisi, was working on microarrays in Pat Brown's lab, and to me that seemed like the next logical step to take in Cynthia's field, insulin signaling and aging.

Cynthia had studied nematode worms with mutations in *daf-2*, the gene that encodes the insulin receptor. They live twice as long as normal worms, but their longevity is totally dependent on the transcription factor DAF-16. I decided to use microarrays to look at the downstream targets of DAF-16.

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Coleen Murphy

This was right at the beginning of microarray technology…

I had to build hundreds of my own microarrays and then use something like 70 of them for just this one project. Later, I helped teach the Cold Spring Harbor microarray course, but then we stopped teaching it because we very quickly made ourselves obsolete. I think that Pat and Joe may have taught the first class in '97 or '98, and 2005 was the last course because it just wasn't necessary anymore. By now, microarrays are so easy and inexpensive that I have my undergrads—even freshmen and sophomores—do them.

Did you plan to follow up on the DAF-16 work in your own lab?

The very first grants I wrote proposed to study the downstream targets of DAF-16.

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But they weren't funded, and, frankly, in retrospect, those projects would've been pretty boring anyway. Fortunately, I had a year to think about what I was going to do before I started my own lab. My husband, Zemer Gitai, and I had both been offered jobs at Princeton, but he was a year behind me and had to finish another year of his postdoc before we could move. So I started wondering if I should start something brand new. I came up with the ideas for two other projects and applied for—and won—several young investigator fellowships. That was great, because those fellowships gave me the latitude to strike out and try something new.

OLD AGE PROBLEMS

What were those two projects?

One thing I wanted to do was to look at how long-term memory is affected by age and the other was to look at reproductive aging—that is, how long the animals are able to produce viable offspring. When we first started, it wasn't clear that *C. elegans* would be a good model for reproductive aging, but it turns out they are. One of my graduate students, Shijing Luo, did microarray studies that showed that the genes that decline with age in worm oocytes are the same genes that were known to decline in mouse oocytes, so oocyte aging in both organisms seems to be largely regulated by the same pathways.

PHOTO COURTESY OF COLEEN MURPHY

Murphy and husband, Zemer Gitai, indulge in their favorite hobby.

We showed that one thing that's altered in both organisms is TGF-β gene expression, which goes up with age. There are two TGF-β pathways in worms, and we showed that only one of them, the Sma/Mab pathway, tells the animal how long to keep its reproductive system healthy. Mutants in this pathway control a whole set of genes that would normally decline in wild-type animals with age and instead prevent them from declining, resulting in better oocyte quality.

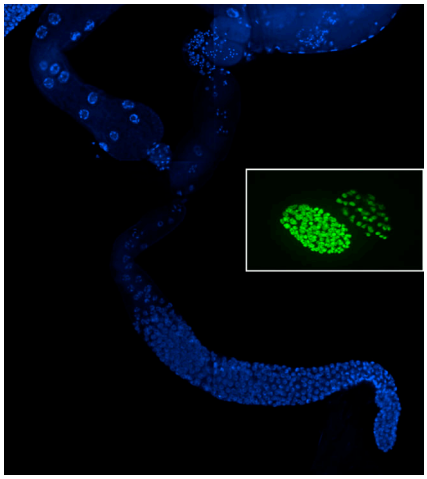
> "When we first started, it wasn't clear that worms would be a good model for reproductive aging."

In calorically restricted animals or insulin receptor mutants, on the other hand, somatic and reproductive lifespans are both extended. But TGF-β mutants are funny because their reproductive systems look fantastic but their bodies keep aging, so their somatic and reproductive lifespans are uncoupled. The end result is disastrous, because those worms often die when their aging bodies can no longer give birth to their offspring. There may be other things that regulate reproductive lifespan but that don't affect somatic lifespan, and that is something we're looking into now.

How do you measure cognitive decline in a worm?

A worm is basically designed to reproduce, and to do that they have to get enough nutrients. They can smell, so we decided to ask, if there's an odor that we know the worms can sense, can we pair that in a Pavlovian manner with food they really like? Then, we asked how long they remember that stimulus–reward pair and how that changes with age. We showed that, in worms, long-term memory is largely dependent on a gene called Creb, which is not so surprising, because that's been shown in a lot of other organisms. It turns out that Creb levels fall with age, and the first thing aging animals lose is the ability to form long-term memories.

In both wild-type and long-lived *daf-2* mutants, Creb levels fall at about the same rate. But interestingly, calorically restricted animals preserve long-term memory for longer, even though they're less good at learning in the first place. So now, we'd like to know if there's some other mutation that extends both lifespan and long-term memory.



IMAGES COURTESY OF SHIJING LUO AND COLEEN MURPHY

Healthy oocytes (inset, in green) are abundant in old *sma-2* mutant worms (germline nuclei highlighted in blue).

What about life outside of the lab?

I used to have hobbies, and now I have kids. [Laughs] But I'm okay with that! I feel that women often talk themselves out of staying in science because the prospect of having both a family and a career can be somewhat daunting. It would be easier if universities helped provide more access to daycare, but it's not impossible. You just have to prioritize.

My husband and I have two kids, and our hobbies are doing stuff with them, which is a lot of fun. We're total nerds, and we're forcing our kids to be nerds, too. Our eldest already knows what GFP is, and he loves worms. He's already told us he's going to do his PhD, but he's not sure what he wants to write his thesis about. [Laughs]

1. Murphy, C.T., R.S. Rock, and J.A. Spudich. 2001. *Nat. Cell Biol.* 3:311–315.
2. Murphy, C.T., et al. 2003. *Nature*. 424:277–283.
3. Luo, S., et al. 2009. *PLoS Genet.* 5:e1000789.
4. Luo, S., et al. 2010. *Cell*. 143:299–312.
5. Kauffman, A.L., et al. 2010. *PLoS Biol.* 8:e1000372.