# Alison Frand: Breaking out new ideas on molting

Alison Frand is using RNAi, GFP-PEST, and other state-of-the-art tools to study molting in worms.

The nematode worm, *C. elegans*, sheds its exoskeleton at particular life stages, and Alison Frand believes that understanding this molting process might provide new insights into diseases affecting humans. Some of the potential medical benefits lie in the similarities between the worms' exoskeleton and our own skin and connective tissues, while other benefits might lie in the unique aspects of worm molting.

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Frand loves worms. But this love affair didn't start until her postdoc years in Gary Ruvkun's lab. Before that, as a Ph.D. student at MIT, she was happily married to protein disulfide bond formation in yeast (1–3). Then, in Ruvkun's lab at Harvard, she worked on a landmark study using a reverse genetic screen to identify and characterize the genes involved in worm molting (4). And there was no looking back.

Now, armed with the results of that screen, Frand is continuing her work on molting at UCLA (5), where she heads her own lab. We pinned her down to ask about how she, as a young scientist, shed her protein biologist skin and became interested in molting.

## BIOLOGY ALL THE WAY

***What first got you interested in science?***

I first got interested in science in middle school. I had a teacher named Sharon Sicher, who mentored a whole group of students in an after-school science program.

Then, in high school, I had another mentor, Dr. William Ritter. The dedication of these teachers really nurtured my interest in science and my sense that it was a rewarding endeavor and something I wanted to keep doing.

***Were you always interested in a career in biology?***

Always biology. And I think my experiences have really built on each other. First, I was interested in marine invertebrate zoology—in high school, I thought I wanted to study water bugs. Then, as a biology major at Cornell, I did an undergraduate project on translation in mitochondria with Tom Fox. Working in Tom's lab prepared me to work on protein folding at MIT, and I think the work at MIT prepared me to develop an independent project on the molting cycle in my postdoc. All along, I was fortunate in finding really great training environments and really outstanding mentors.

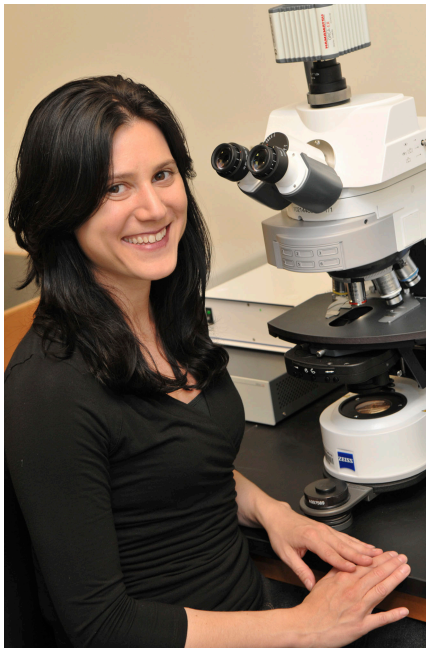
***What draws you to doing research?***

I have such a sense of joy at my bench. I like to form hypotheses and test them. I like to see the data, to know whether or not the way I'm thinking about something is right. It's a very gratifying experience. And if the data tell you something is working in a different way than you imagined, in that case there's more to learn. I love the process of always asking the next question, continuing to go deeper and continuing to see how much of a problem we can understand. Being at the bench is my path to that experience.

## A NATURAL EVOLUTION

***How did you arrive at studying protein disulfide bond formation as a graduate student?***

When I chose a graduate lab, I was looking for the right mentor. I had taken a graduate biology course with Chris Kaiser called Methods and Logic, and I saw him as someone with a tremendous set of scientific skills. He was still relatively new at the time, and I specifically wanted to work for a younger PI who was active in the lab. I also wanted to work in a system where I thought that I could learn a whole lot of techniques. Yeast was a great training ground—I learned genetics, cell biology, and biochemistry. I thought that if I had a broad set of skills, I would be in a good position to tackle whatever scientific questions came later.



Alison Frand

When I joined Chris's lab, the focus was the study of the secretory pathway. The lab was doing screens to find new secretory mutants, and I started out identifying the genes that were defective. One of the genes that I cloned turned out to encode an enzyme that catalyzes the formation of disulfide bonds. Without it, some proteins don't fold properly and get held back in the endoplasmic reticulum. This discovery was exciting because at the time there was a beautiful body of work studying disulfide bond formation in vitro, but not as much was known about how disulfide bonds formed in the eukaryotic cell.

***In your postdoctoral work, you moved to a very different field—what motivated the switch?***

When I started looking for postdocs, I really wanted to ask questions about biology at the level of the organism. I found the molting cycle of nematodes

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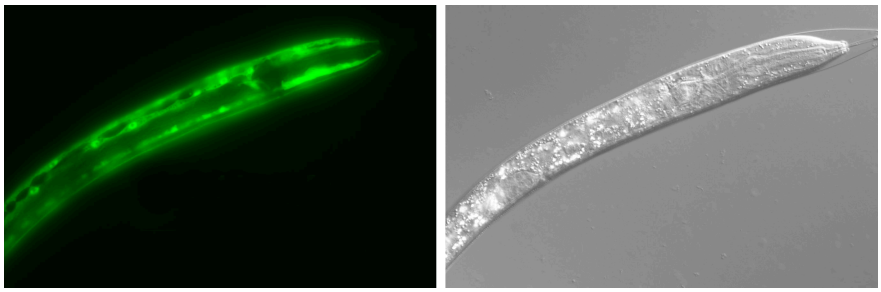
fascinating. *C. elegans* has an external skeleton made of collagen. It's similar to human skin and connective tissue, and it serves many of the same functions as our skeleton. As worms develop, once every eight hours they take apart this elaborate skeleton and make a new one. That process of renewing the skeleton has to be coordinated in epidermal cells all over the body. The animal also has to integrate sensory and physiological cues to know when to execute the renewal. It's really very exciting.

The reverse genetic screen we did in Ruvkun's lab identified many of the genes required for the worm to shed the skeleton. Some of the genes were found only in nematodes, and so they may represent new drug targets for diseases caused by parasitic nematodes. Such diseases currently affect 140 million people in tropical regions.

We also found genes that encode enzymes and matrix proteins homologous to vertebrate proteins. For example, one of the genes encodes the orthologue of human fibrillin, a component of extracellular matrix fibers that's defective in Marfan's syndrome.



**A GFP reporter shows expression of the *mlt-11* gene during molting.**

## LOOKING TO THE NEXT STAGE

***Your screen for molting genes involved introducing RNAi to the worms by feeding them modified bacteria?***

Yes. We feed the worms bacteria that make double-stranded RNA matched to a particular worm gene. The worms eat the bacteria, the RNA gets in their gut, and then it spreads throughout the body, silencing the gene. The bacterial library was made by Julie Ahringer's laboratory, and the Ruvkun lab was very fortunate to receive the library relatively early. Genome-wide screens were a new approach. As a graduate student, I had worked on one gene. So it was a real shift in thinking, coming to a place where you could look at the whole genome. And then you have to go on to ask what you can do with the genomic information once you have it.

***How did you know when you were ready to move on to the next step in your career?***

As a postdoc, I got to focus on a new scientific question. When *PloS Biology* published my paper, I felt that I had made progress on that problem. That's when I felt I was ready to start my own lab. I don't know if anyone ever feels totally prepared to become the head of a lab, but I'll do the best I can.

**Loss of *C. elegans acn-1* (bottom), the homologue of human ACE, prevents molting.**

***What problems are you focusing on now in your own lab?***

There are two major questions that we're studying. We want to understand how neuroendocrine circuits regulate the molting cycle as a model for the hormonal control of development. So, we want to understand how physiologic signals trigger or repress remodeling of the skeleton, and how the worm's behavior is coordinated with the molt. Our other major focus is to understand the molecular mechanisms for remodeling the skeleton. Ideally, we'd like to know what every membrane protein and every matrix protein uncovered in our screen has to do when it's time to make a new skeleton, and how the proteins work together to accomplish that task.

**"I am so excited to be here at UCLA, starting a lab and watching it grow."**

I am so excited to be here at UCLA, starting a lab and watching it grow. You get to a point where you have so many ideas that it's not possible for you to research them on your own, and you need a group of people working together to explore and expand those ideas and take the work in new directions. I hope that my interactions with graduate students honor the commitment of my mentors. If I could be as good a mentor as the ones I've had, that would feel like a significant contribution. JCB

1. Frand, A.R., et al. 1998. *Mol. Cell.* 1:161–170.
2. Frand, A.R., et al. 1999. *Mol. Cell.* 4:469–477.
3. Frand, A.R., et al. 2000. *Mol. Biol. Cell.* 11:2833–2843.
4. Frand, A.R., et al. 2005. *PLoS Biol.* 3:e312.
5. Hayes, G.D., et al. 2006. *Development.* 133:4631–4641.