Amy Kiger: Abuzz on cell biology

Kiger is probing the genetic factors underlying cell shape and cell growth using genome-wide screens, imaging, and in vivo studies in *Drosophila*.

From flattened epithelial cells to elongated neurons, cell morphology is heavily intertwined with cell growth and function. Understanding the genetic factors that govern cell shape might therefore provide insights into the processes underlying development and disease.

Amy Kiger has focused on these and other fundamental questions of cell biology in *Drosophila* throughout her career. She first worked on circadian rhythm in *Drosophila* as a research technician in a laboratory at The Rockefeller University, then studied male germ line stem cell biology in flies as a graduate student at Stanford (1, 2). Her postdoctoral studies in Norbert Perrimon's laboratory at Harvard on the genetic basis of cell morphology and growth in *Drosophila* have yielded several novel insights (3–5).

"I did wonder, 'Would anyone really care about what happens in the flies' testes?'"

With the results of these massive genome-wide screens (5), Kiger is now striking out on her own at the University of California, San Diego (UCSD), investigating the genetic basis for cell shape in her favorite model system—the fruit fly. She discussed with us the dizzying possibilities presented by her work.

THE MOST IMPORTANT THING

What got you interested in science?

I think science was always the most important thing for me even though I hadn't quite formally put my finger on it initially. But when forced to think about a career, stripping away everything else that wasn't important was easy for me: what I was left with was a desire to understand life, which was an interesting and challenging prospect. I didn't have any life-changing moment, but just an ever-present interest in science because of the opportunity for having a very challenging and fun job.

How did you decide to do a PhD after getting your undergraduate degree?

It really seemed like the only interesting route for a career. After leaving college, where things seemed a little more abstract, I was left with, "How am I going to make this into a living?" All the other options sounded so unappealing to me. I didn't want to be a doctor, but I enjoyed research. But before going down that route, I wanted to take some time off and get more research experience before applying to graduate school. So, I worked at Rockefeller as a technician in Mike Young's laboratory for about a year. It was a good training ground for me to see what was possible.

COMPLEXITY AS A VIRTUE

What drew you to Margaret Fuller's laboratory at Stanford for your PhD?

I tried other things during my rotations in graduate school; I was very interested in host–pathogen interactions, for example. I was also really interested in stem cell biology questions, which I pursued for my dissertation work. I think I was drawn to the complex biology of stem cells, which don't exist on their own, but are part of a niche. And there's this complexity of interplay between the stem cell and its niche.

I was drawn to functional approaches and genetics as well. My "aha" moments usually come at the beginning when I observe interesting new phenotypes. Margaret's laboratory had a few *Drosophila* mutants they didn't know much about that seemed to lose their stem cells or not maintain gametogenesis. I was interested in those types of problems because in the fly, we could actually look at stem cells and apply genetics to the problem. Looking around at the state of the field at the time, I realized people weren't really studying stem cells with genetics. No one had identified a single gene about which they could say, "Yes, this gene is important for stem cell behavior." So that's what drew me there: the promise that with the *Drosophila* system, we could answer those types of questions.

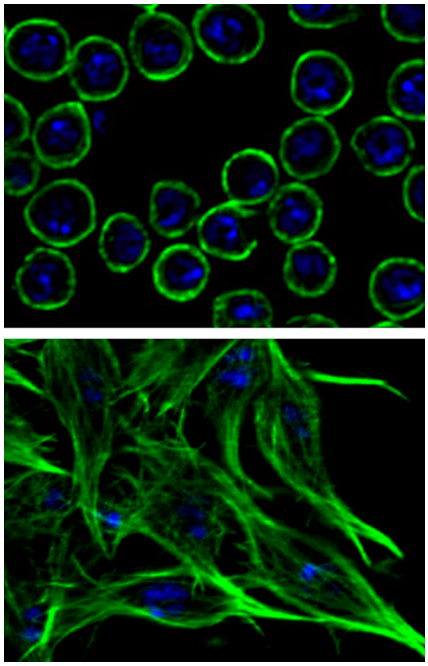
Amy Kiger

Was it lonely working in this field on a problem like that?

I felt a little isolated at the time because there weren't a lot of people in *Drosophila* working on male germ line stem cells—people that I could talk to who knew this tissue type. What meetings do you go to when there's a field of two or three laboratories? That's not a conference. So I remember feeling very frustrated that there weren't stem cell biology meetings. But there are stem cells in many tissues, and stem cell biology is a big problem that people had been working on for a long time. On the one hand, I felt that we were beginning to tap the understanding of these problems. Also, in the bigger picture, these problems were related to many other systems and to bigger questions.

Because it was early days, I did wonder, "Would anyone really care about what happens in the flies' testes?" But I guess perseverance is a good attribute for scientists, because this system has proven to be really good for looking at what stem cell behaviors arise in stem cells themselves, and which of these behaviors are directed by the cells' environments. It's been very useful for uncovering ways in

Text and Interview by Caitlin Sedwick
csedwick@gmail.com



An RNAi screen (top) identified genes required for cellular elongation.

which a niche can be regulated, and whether this kind of regulation is also used in other stem cell niches.

What was your postdoctoral project with Norbert Perrimon?

When I finished my dissertation, I still thought that I would continue to think about some stem cell biology problems. But I also wanted to get inside a cell and think more about cell biology. The project I worked on in Norbert's laboratory evolved after I arrived. I used RNA interference (RNAi) on *Drosophila* cells in genome-wide screens for genes that affect cell morphology and fitness. Before my arrival, Norbert had already started thinking about applications for RNAi in *Drosophila*. Because his laboratory was very crowded, my desk was in his office along with that of another postdoc. Maybe it was that proximity, with me sitting there in my first couple weeks, which convinced me to consider doing these screens. Like before, I was excited by the prospects for this approach, as I had the feeling that people really weren't yet studying cell morphology in a dish this way.

I didn't have a specific pathway or question that I wanted to target when we began working on the screens. My initial goals were to establish a widely applicable method and to perform "foundation screens" for discovery of future work. And in fact, the project had a somewhat smaller scope until we started to go a little deeper, when we began to see the potential for these screens to uncover new phenotypes. As we started to work on the system, we realized that the best way to approach the work would be to design something similar to the patterning screens from embryo development in *Drosophila* that we all revered. We needed to start with screens to examine the phenotypic space in these cells. We would eventually get back to the things that we conceptually knew should be causing changes in phenotypes, but this approach would also give us a sense of what we were missing or unaware of.

READY FOR THE FUN PART

What has been your biggest challenge in your work so far?

During the early part of my career, like in my graduate and postdoctoral work, it was having the confidence and the perseverance to stick with what I saw as important problems, despite being in a small field or doing things in a new way. The challenge now is in running my own laboratory, and in constantly managing a bigger vision with what needs to be done day-to-day: the stepwise process of building my own laboratory, and the new systems that we're working on here. I personally find it challenging that although we are making progress, it doesn't all happen at once.

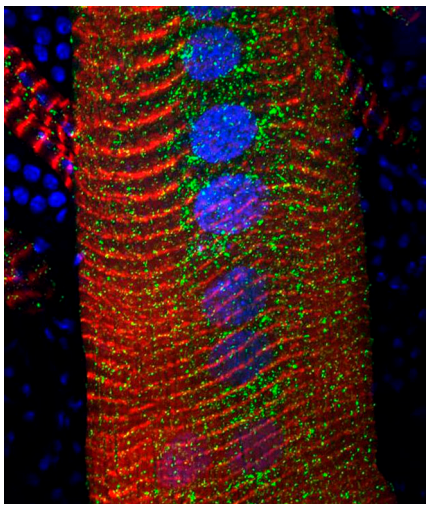
Which aspects of your previous work have you chosen to follow up on in your own laboratory at UCSD?

We're working on modifier screens to find gene functions that enhance or suppress cell shape phenotypes. We're currently thinking a lot about lipid signaling and phosphoinositide regulation. It's clear that different phosphorylated forms of phosphatidylinositol are temporally and spatially localized, and this seems to be related to the problems in cell morphology I've always been interested in, like how cells remodel and change their shape. Because the bioactive molecule here is something that's metabolized and not encoded in the genome, it presents a really interesting problem in decoding the phenotype. Perhaps we're knocking down a gene that directly regulates phosphoinositide levels, or a gene that encodes a protein that responds to phosphoinositides. We can begin to build whole pathways that are important for the phenotypes that we are following.

"I personally find it challenging that although we are making progress, it doesn't all happen at once."

We're almost to the point where we're raising more questions than we answer. We've built a lot of new tools, mutants and reagents to study these problems, and we have the infrastructure to do screens. We have so much to work and play with now. We're ready for the fun part. JCB

1. Kiger, A.A., et al. 2000. *Nature.* 407:750–754.
2. Kiger, A.A., et al. 2001. *Science.* 294:2542–2545.
3. Kiger, A.A., et al. 2003. *J. Biol.* 2:27.
4. Eggert, U.S., et al. 2004. *PLoS Biol.* 2:e379.
5. Boutros, M., et al. 2004. *Science.* 303:832–835.



The phosphoinositide PI(3)P (green) is dispersed among the actin filaments (red) in *Drosophila* muscle.