# People & Ideas

## Denise Montell: Lighting the way in border cell migration

Montell studies *Drosophila* oogenesis, focusing primarily on the collective migration of border cells.

During *Drosophila* oogenesis, a group of cells breaks off from the epithelium that envelopes the egg chamber. Squeezing between the gigantic nurse cells, these so-called border cells migrate from the anterior end of the egg chamber to the posterior, where they subsequently form a pore in the developing eggshell.

Denise Montell has been studying this process for much of her career (1). Along the way, her lab has generated important insights on topics ranging from epithelial-to-mesenchymal transitions (2) to collective decision-making in cell migration (3, 4) to organ shape sculpting (5). We reached her at her laboratory at the Johns Hopkins School of Medicine to discuss how border cells fulfill their developmental destiny and how she determines her own fate.

### COLLECTIVE EFFORT

***What drew you to a career in science?***

Both my parents were scientists, which makes it sound like I was lacking in imagination when I chose my own career. But in fact, as a child I didn't especially want to follow in my parents' footsteps. The guiding principle for me was really that I was curious about things. That kind of inquisitiveness naturally takes you into science, because other disciplines don't seem to be as much driven by simple curiosity.

In college at UCSD I majored in biochemistry, but I remember feeling that the basic biology classes on genetics and developmental biology were rather boring—which is ironic considering what I ended up working on in my career. The real turning point for me, when I knew what I wanted to do, was when I took an advanced neuroscience class from Nick Spitzer at UCSD. Nick is an incredibly charismatic teacher. He's absolutely excited about what he's teaching. It just grabbed me instantly, and I decided to go to graduate school in neuroscience because I had had such a wonderful experience in Nick's class. I did my graduate work on *Drosophila* neuroanatomy with Corey Goodman, who had done a postdoc with Nick and who has some of that same charisma.

***When did you first start working on border cell migration?***

A lot of the effort in my lab over the past 20 years or so has been focused on this small group of cells that undergo a particular migratory program. I started out working on this when I was a postdoc in Allan Spradling's lab doing a *P* element–mediated mutagenesis screen in *Drosophila*. Allan was one of the two scientists who developed this technique, and this was the first large-scale transposon mutagenesis screen that had been done. All the postdocs and the one graduate student in the lab collaborated in this huge effort to generate more than 10,000 *P* element mutant lines.

This screen went on for months, 24 hours a day, seven days a week. I was an early morning person, so I was on the 8:00 a.m. shift. The screen was very productive in general, but only one mutant out of the 10,000 had a border cell migration defect. That suggested that probably a lot of the genes I was interested in were mutating to lethality.

> "We keep uncovering new surprises; it never gets boring."

To get around that problem when I started my own lab, we took other strategies like mosaic lines and so on. And each time we screened using a different approach, we'd find new mutations, new genes, and whole new pathways involved in the process. We keep uncovering new surprises; it never gets boring. That's why I've kept studying this process ever since.

PHOTO COURTESY OF AMANDA MONTELL

**Denise Montell**

### DECIDING TO LEAD

***What are some of the major molecules involved in border cell migration?***

During oogenesis, the egg chamber is surrounded by an epithelium of about 650 follicle cells, and there's a special pair of cells at each end of the egg chamber called polar cells. The polar cells secrete a ligand that activates the JAK/STAT pathway in neighboring cells. At the anterior end of the egg chamber, cells with high JAK/STAT activity become border cells. Border cells then migrate as a group from the anterior of the egg chamber toward the posterior, stopping when they reach the oocyte.

Border cells retain apical/basal polarity, and they retain certain hallmarks of epithelia such as E-cadherin expression while they're migrating. So they have a morphology that's partially epithelial and partially mesenchymal. But STAT is absolutely critical to both the acquisition and maintenance of the motile phenotype. If you interrupt JAK/STAT signaling after border cells have initiated migration—for example, using a temperature-sensitive allele—then the cells lose expression of certain border cell markers and regain

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markers representing those cells that remain in the epithelium. So, their fate as migratory cells is not completely stable; you need sustained JAK/STAT signaling to ensure that the cells maintain their motile phenotype throughout their migration.

***What role do small GTPases have in this process?***

Another thing we discovered—back in the mid-1990s—was that the small GTPase Rac was required for border cell migration. The experiment we really wanted to do was to see if locally activating Rac would be sufficient to steer border cell migration, but for many years it wasn't possible to do that. You could express a constitutively active form of Rac everywhere in a cultured cell, and the cell would ruffle all over the place, but they didn't migrate in one particular direction. Moreover, border cells expressing constitutively active Rac can't migrate at all, suggesting that Rac activity has to be regulated, either spatially or temporally or both. Then Yi Wu and Klaus Hahn had the brilliant idea of taking a light-sensing domain, called the LOV domain, from a plant protein and fusing it to an active form of Rac in such a way that, in the absence of light, it obscures Rac's effector-binding domain. But if you illuminate it with blue light, it undergoes a conformational change that allows Rac to become active and interact with its effectors.

PHOTO COURTESY OF DENISE MONTELL

**Montell and family visit the Wadi Rum Desert in Jordan.**

Using this construct in intact egg chambers, we were able to use a laser to activate Rac in one border cell and then observe that the whole group of cells would follow the laser. It's kind of like a video game, where you can get the cells to chase after the light. When you activate Rac in one border cell, the neighboring cells retract their protrusions and decide to follow that cell. We're very interested in understanding how that signal is communicated from the targeted cell to adjacent border cells.

## IMPORTANT PARTNERS

***What other projects are active in your lab right now?***

We're working on various aspects of border cell migration, and that'll probably always be a big focus for us because the more we learn, the easier it is to learn even more. We're exploring a number of avenues, including several projects that focus on new bio-manipulation tools and bio-sensors for different protein activities. We also have a couple of projects in the lab that are not at all oriented towards border cell migration but that focus instead on other aspects of oogenesis, which serves as a great model for how any organ or tissue develops.

> "The whole group of cells would follow the laser... kind of like a video game."

Almost every project in my lab right now builds on a really important technique developed by Mohit Prasad when he was a postdoc in my lab. He discovered how to culture egg chambers outside of the female fly, which opened up the entire world of live imaging to us in the study of border cell migration and of many other events in oogenesis.

***How has your decision to have a family impacted your career?***

I will say it was definitely the hardest thing I've ever done, but it was completely worth it. The main challenge for me, because my husband and I both run research labs, was finding really good, affordable daycare when our kids were little. It was really almost impossible. We got through those periods, but a key reason why I was able to finally succeed in having a career and a family is that my husband was definitely willing to pull 50% of the weight when it came to household and childcare duties.

Now my oldest child is a sophomore in college, and my youngest is starting university. Looking at the empty nest, I'm glad I have my career (and all the administrative work I've taken on) to occupy me. Otherwise, I think the nest would feel even emptier. There are some nice things about them getting older, though. For example, we're able to travel together as a family more often, and they bring home all kinds of interesting new ideas. My kids will definitely continue to enrich my life.

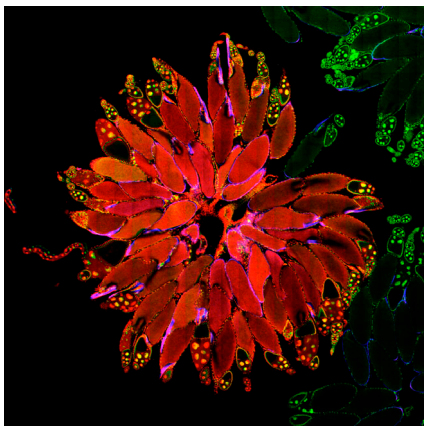

IMAGE COURTESY OF HOGAN TANG, USING A MICROSCOPE PROVIDED BY NIKON

**A *Drosophila* ovary spread out on a slide, one of the top images in the 2011 Nikon Small World microscopy contest.**

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4. Wang, X., et al. 2010. *Nat. Cell Biol.* 12:591–597.
5. He, L., et al. 2010. *Nat. Cell Biol.* 12:1133–1142.