People & Ideas

Yohanns Bellaïche: Mastering multiscale morphology

Bellaïche uses physics and genetics to study tissue morphogenesis.

As embryonic tissues develop toward their adult state, they experience enormous changes in both form and organization. As Yohanns Bellaïche can readily attest, these changes result from the collective effect of many seemingly minor shifts in a signaling pathway or in cytoskeletal organization of individual cells that together cause the dramatic rearrangement of entire tissues.

Bellaïche completed his graduate studies on classical problems in developmental biology, such as the establishment of morphogen gradients (1). But, later, the emergence of new technologies enabled him to ask entirely new kinds of questions about how cell biological processes drive organ development (2). Now Bellaïche's lab is at the forefront of yet another revolution in developmental biology. He is adapting approaches from the physical sciences to investigate the cell-level changes that underpin the large-scale movements of tissue morphogenesis (3–5), as we learned when we called him at his lab at France's Institut Curie.

THE FLY EFFECT

Were you interested in biology as a child?

I was more interested in math and physics. I think those subjects are more highly prized than biology in the French school system, but even once I reached lycée—the French equivalent of high school—I was not at all interested in biology because the way it was taught was more about classification or ecology. It was very descriptive and didn't involve much molecular mechanism.

In France, one can either go directly from lycée to a public university or take another few years of education in classes préparatoires. Then one can take the competitive exams and apply for admission into the grandes écoles—the "elite universities." I was lucky because, even though my family was not rich, the French public schools are free and very good, and I did well enough in my studies that I went ahead with classes préparatoires. I only became interested in biology in my last year of prep school, when my classes started to explore physiology and cell biology in molecular detail.

How did you arrange to do your master's degree with Claude Desplan in New York?

It was more Claude who arranged it. He's a big figure in the fields of *Drosophila* genetics and development, and he's also French. I think he wanted to keep some connection with France, so every year he would recruit a few students from my grandes écoles to join his lab for one or two months. I had learned about fly developmental biology in school and was very interested in working on this, so I went to his lab for two months and then decided to stay for a year to do my master's. At the end of this, I had to go back to France for my military service, but I knew I wanted to do a PhD. So then I joined Norbert Perrimon's lab at Harvard.

> "I always have a secret project...that's a little bit of a crazy idea."

I think Norbert is similar to Claude; he is also French and is happy to have French people in his lab. This was good for me because my English was still not so good! [Laughs]

CAREER CASCADES

What did you work on with Norbert?

When I arrived in his lab, Norbert had this idea that we should develop methods to do homologous recombination in the fly. I was very interested in this, but it was an extremely risky project. So I asked Norbert if he had another, safer project that I could also work on. He was very generous and gave me one of the genes that came out of a large screen for new regulators of morphogen signaling.

It was good I had this other project, because the homologous recombination project did not go very well. Actually, what I was doing was exactly what we do now to accomplish homologous recombination in the fly, but I made one mistake: I tried to do it in male flies. If I would've chosen to do it in females, it would've worked, but it did not work so well in males. Fortunately, my backup project was very successful. We discovered that the gene I was working on was involved in regulating the range of the hedgehog morphogen.

PHOTO OF PEDRO LOMBARDI (INSTITUT CURIE)

Yohanns Bellaïche

In your postdoc you started working on cell polarity…

I returned to France and joined François Schweisguth's lab for my postdoc. At the time, there was a big transition in the developmental field because new imaging methods were starting to become available that let us image individual cells within tissues. Also, RNAi had been discovered and could be widely and easily used with in vitro cell culture models. I remember thinking that these tools would mean the end of in vivo studies because we could now do genetics in vitro. But I was wrong! These technologies instead helped in vitro and in vivo studies to become more complementary, greatly advancing our understanding of the cell biology of development.

In François' lab, I was working with a great postdoc named Michael Gho, trying to develop a system to observe fly mechanosensory organ development. This was the early days of confocal microscopy, so there was no way to automate a time-lapse image series. I sat there pressing a button to take

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a picture every four minutes for 12 hours, but in the end we got these beautiful images and learned exciting new things about the development of this organ. From then on, it was clear to me that this was what I wanted to do: combine microscopy with genetics.

What was most interesting to me was that we discovered how cells within a tissue can sense the overall axes of symmetry within the body. In the mechanosensory organ, as in other tissues, asymmetric cell division guided by these axes allows cells to take on different fates important for organ development. But if you remove the mechanism that senses the axes, the cell will still become polarized and divide asymmetrically, so there is a symmetry-breaking mechanism intrinsic to the cell. From there, we simply reanalyzed the functions of genes known to be involved in asymmetric cell division in other systems. We discovered that many genes involved in epithelial apical/basal polarity are also involved in development of the mechanosensory organ, but cell polarity is rotated by 90 degrees along the apical–basal axis.

A MATTER OF SCALE

In the past few years you've shifted your emphasis toward the mechanics of tissue morphogenesis…

I always have a secret project in my lab—one I start on my own—that's a little bit of a crazy idea. If it seems like it's going to work out, I give it to someone in my lab to work on. Five years ago, I was quite lucky to get a European Research Council grant to fund my latest secret project and to hire the physicists I needed to start working on it.

PHOTO COURTESY OF YOHANNS BELLAÏCHE

Bellaïche and a lab member share a moment of discovery with an excited five-year-old.

The idea of the project was to move from single cell polarity to global tissue polarity.

When you go from thinking about a single cell to thinking about a tissue, you encounter what we call the multiscale problem. You have to link processes that occur at different scales: what's happening at the cytoskeletal level, then at the cellular level, and then how this impinges on something that takes place at the global level. For example, tissue deformation or tissue shaping is a result of the action of multiple pathways, such that very tiny changes at the level of individual cells can collectively generate very large-scale changes at the tissue level. This is evident from some of our recent work, where we showed how the myosin Dachs controls morphogenesis and showed that loss of the protein PTEN destabilizes cell–cell junctions by affecting myosin distribution, thereby affecting how cells pack together pack together in an epithelial sheet.

Another story I like a lot involves the formation of new junctions in tissues. When a cell divides alone in a petri dish, a tiny junction—just a dot, really—forms between the two daughter cells. But in tissues the two daughter cells create a very long junction between them. We showed that, if you ablate a dividing cell's neighbors within a tissue, the junctions between daughter cells are tiny, just like the ones you see in a petri dish. I think that's quite interesting because it tells you that the neighbors play an important role in determining how the cell divides; the unit of a tissue is not just one cell but the cell and its immediate neighbors.

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Now we are very interested in understanding how intercellular adhesion, which is regulated by the cytoskeleton, allows for self-organization of a tissue. We also want to examine how gene expression patterns affect morphogenesis. To do this, we'll need to make use of statistics and machine learning to analyze the measurements we can get from classical biology.

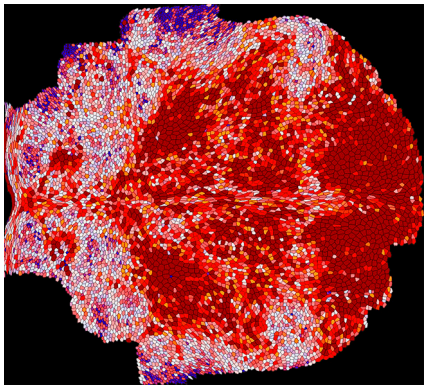

IMAGE COURTESY OF FLORIS BOSVELD AND BORIS GUIRAO

A segmented image of *Drosophila* thorax showing individual cells (color-coded according to apical size) participating in morphogenetic movements.

Do you have any advice for people just starting out in the sciences?

I always advise my PhD students to replicate the experiments that form the foundation of their project. By redoing these experiments, they'll learn exactly what the actual results were, what their interpretation was, and what assumptions were made. They will have a much better grasp of their system and the subject before they start on their own project.

Unfortunately, there are fewer and fewer PhD students embarking upon biological studies in France right now. One way we could change that is if we get kids interested in biology early on. For example, when my daughter was five years old, I invited her and her classmates to visit my lab for some science workshops. We talked about what defines a living organism, we isolated DNA, we did chromatography, and the kids were excited about all of it. They absolutely loved it! I think it's amazing that you can teach things like this to kids so young, and we're definitely going to do it again.

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