Bob Goldstein: Cell biology by way of development

Goldstein is studying the cell biology of how organisms develop.

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Bob Goldstein

Cell–cell interactions, asymmetric cell divisions, and cell movements set the foundation for the development of complex body forms. But the cellular processes underlying these phenomena are still being investigated.

Throughout his career, Bob Goldstein has worked to (literally) dissect the mechanisms of embryonic development using *C. elegans*. His early work, showing how cell–cell interactions drive specification of the worm endoderm and mitotic spindle orientation (1, 2) and how the point of sperm entry determines the developmental axis of the new embryo (3), has become part of the canon of the field. Since then, Goldstein's interests have continued to develop along new axes (4–5), as we heard when he spoke with us from his lab at the University of North Carolina at Chapel Hill.

A FORMATIVE TIME

What guided your early career choices?

In college I took a class with Ray Rappaport, a father of the cytokinesis field. Throughout the class, he'd give some background to an interesting scientific question. Next, he'd discuss a clever experiment designed to answer that question, and then he'd tell us the results. I think that's when I first realized that doing science is a creative activity; it's not just compiling facts. Experimental design involves a lot of creative energy.

I decided I wanted to try graduate school. Ray recommended a few people, given my interests, that I should consider training with, and one of them was the person whose lab I ended up joining.

Ray died just a couple of years ago. I keep a little shrine to him in my lab's microscope room. There's a picture of Ray, a sand dollar—he often used sand dollar embryos for his studies—and a glowing set of LED lights.

> "Experimental design involves a lot of creative energy."

So you joined Gary Freeman's lab at The University of Texas based on Ray's advice…

Yes. Gary was a well-known embryologist who'd done some great experiments. He kept a really small lab, and he didn't assign projects. He didn't even really have organisms for us to work with. When I arrived, he said, "So what do you want to do?"

I tried all sorts of experiments in all sorts of organisms, and he was very patient with how naïve I was and with my bouncing back and forth between being very engaged and very frustrated. I was almost two years into grad school before my first experiment worked.

What was that first experiment?

I tried doing some old-fashioned embryology with *C. elegans* embryos. There was a claim in the field at the time that there weren't many cell–cell interactions guiding embryonic development in the worm embryo. The best way to test this was with cut-and-paste embryology: separating the cells from each other, asking whether they now behave differently, and then placing them back in contact to try to rescue any lost behaviors. But no one had really done that in *C. elegans*.

I tried taking envelopes off of *C. elegans* embryos for a while and managed to get very few cells out. And they just wouldn't develop. Then I learned that Lois Edgar, in Bill Wood's lab in Colorado, had already developed a method for removing egg shells and culturing separated cells. So I went and visited her. She was really generous and taught me how to do it. Then I went back to Texas and tried just isolating cells, asking if there are tissues that require cell interactions for them to develop. I started with the gut lineage and found an interaction between two cells that specifies the gut. The paper describing these experiments—I was sole author on it because Gary didn't put his name on students' papers—was published in *Nature*. I felt very lucky. It was hard to let go of the idea that this is how publishing would always work. [Laughs]

SPECIFICATION

In your postdoc, you continued working on this question…

Well, my PhD was very short, mostly because the lab didn't really have any equipment. We had dissecting scopes, one compound scope, and a needle puller, and that was it. So I applied to work with John White in Cambridge, which at the time was a *C. elegans* mecca. My first postdoc was really, in a sense, a continuation of my PhD.

John's lab was very well equipped—he developed incredible new equipment himself—but the day I arrived he told me he had just decided to move to Wisconsin. There were four of us working in the lab, and he left all four of us and all the equipment behind, and we had a headless lab for three years. It was a terrific environment, because there was a really interactive group of *C. elegans* biologists there, and people in the field were really supportive to trainees. In particular, Susan Strome was like an advisor to me. I try to follow her and others' examples in supporting my junior colleagues.

Then, because things had gone well in my PhD and first postdoc, I decided to take a chance on my second postdoc.

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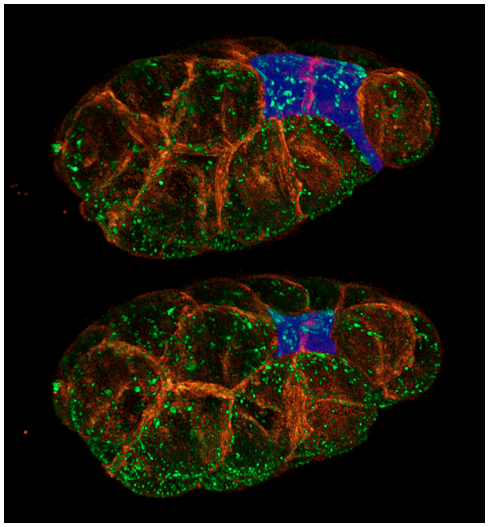

IMAGE COURTESY OF CHRIS HIGGINS AND JIANG GAO

Two stages in the internalization of surface cells (blue) in embryos labeled for plasma membranes (orange) and myosin II (green).

I was interested in how development evolves, and some important studies in that field had used antibodies that recognized key proteins in lots of different species. I had an idea for how to generate antibodies like that, but it failed. Fortunately, I got a job before that failure became apparent to anyone. [Laughs]

So you moved to the University of North Carolina…

Yes, and I went back to *C. elegans* at that point. I set up the lab with the same equipment as I'd had in England. Since that point, I'd say that I've had a clear idea of the direction I'd like things to go, and sometimes they go that way. [Laughs]

Because I'd had such independence in my own training, I like taking on creative, talented people and letting them do what they want. I also encourage them to try out risky experiments. If an experiment only has a ten percent chance of working and would be wildly exciting if it did work, then you only need to try ten experiments to end up with some wild excitement, right?

EXCITING PROJECTS

What are some of the things you've been most excited about lately?

In many ways, developmental biology is a less mature field than cell biology. That forces a sort of 20-questions approach to solving mechanisms—dividing up the world of possibilities from first principles instead of guessing candidate mechanisms. But in the last several years we've moved into the cell biology of development

Just last year we published a paper about how cells move from the surface of the embryo into the center by apical constriction. We had assumed that, when cells move into the center by constricting their apical sides, they trigger movement by turning on myosin motors at just the right time. But what we found is that myosin motors are very active on the cells' apical sides well before constriction happens in both worms and flies. And the cortex under the apical surface is highly contractile and under tension well before the shape change starts. That tells us the trigger for the cell changing shape and moving into the center must not be the activation of myosin contraction but something else. We're now pursuing what that is.

> "Developmental biology is a less mature field than cell biology."

Most of the people who come to the lab now are interested in studying the cell biology of morphogenesis—how animals take shape—using *C. elegans* as a model. For example, we're trying to find mechanisms that are common to *C. elegans* gastrulation and neural tube formation in vertebrates, because that process also uses apical constriction and fails frequently in human development. We're looking at the worm homologues of mouse and human genes known to affect neural tube closure to see if we can identify the cellular mechanisms behind closure defects. We also study how cellular and developmental mechanisms evolve.

So risk taking and creativity have paid off…

I think so. I'm lucky that there are a lot of creative people in my life, both inside and outside the lab. My two brothers are both really creative. One of them builds robots in his spare time, and the other one can make snow. Several times, he's made a few feet of snow on his front lawn overnight.

My kids are also very creative. My wife and I spend a lot of our time on weekends helping our kids to make things that they dream up. We're constantly doing projects, and they seem to get ever more ambitious. My family has actually published protocols for some of our projects in *Make* magazine.

I'm amazed that there's this whole community of tinkerers out there who share ideas and who seem to build upon each other's results in the same way scientists do. I have lots of scientific colleagues who share this interest, and I often end up exchanging ideas with them. It's been terrific to find other parent scientists and talk about projects both in and out of the lab and about strategies for succeeding as a parent-scientist.

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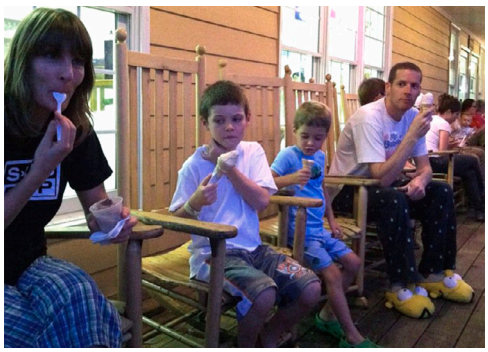

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Goldstein and family