People & Ideas

David Sherwood: Invasive procedures

Sherwood uses a unique in vivo model to study how cells invade through extracellular barriers.

The passage of a single *C. elegans* cell through two basement membranes to connect the worm's uterus and vulva might seem an unlikely model for tumor metastasis. But David Sherwood—who first characterized the process as a postdoc in Paul Sternberg's laboratory at Caltech—thinks that the system can teach us a great deal about cell invasion events in both normal development and cancer.

Sherwood began his developmental biology career as a graduate student with David McClay at Duke University, studying Notch signaling in sea urchin embryos (1–3). After switching to nematodes, he discovered that a specialized gonadal cell, called the anchor cell, crosses the basement membranes separating the uterus and vulva at a specific stage of larval development (4). The anchor cell sends out active processes that attach to the vulval cells while remaining connected to its neighboring gonadal cells, providing a genetically and visually tractable model for examining cell invasion in vivo. It's a model that Sherwood has used to uncover the importance of the transcription factor FOS-1 for basement membrane removal (5) and, having returned to Duke to start his own laboratory in 2005, the role of netrin signaling in orienting the anchor cell to invade in the right direction (6).

> "What we're learning in anchor cells will have broad implications."

In a recent interview, Sherwood helped connect his own life and career, and described how making time for his outside interests keeps him anchored while he pursues further scientific breakthroughs.

EARLY CONNECTIONS

Were you always destined for a career in science?

I grew up in Champaign-Urbana in Illinois, where my dad is a professor in the Physiology Department. He's one of my best friends—we talk every week and of course discuss science together. He has definitely been the biggest influence on my career, but I never grew up envying what he did; I didn't hang out in his laboratory and do experiments.

My dad had a tough upbringing, and he wanted to make sure that we had special experiences as a family. So he'd organize a backpacking trip every summer, usually to the Wind River Range in Wyoming. Dad would hire a horse to drop off our food way beyond where most normal people would backpack. We'd hike up to where the food was and camp there for two weeks. But Dad was both clever and cruel in packing not quite enough food, so we had to catch fish to survive. That's where my intense passion for biology came from: depending upon the fish and starting to see how things are connected in this world.

And that evolved; in my junior and senior year of college, I did a research project with Eli Levine, at the Illinois Natural History Survey back in Champaign-Urbana. He works on the Western corn rootworm beetle, which is a major maize pest, and we ended up publishing a very nice paper where I was the first author. That really cemented my love for biology.

However, I'm sure I wouldn't have become a biologist without the support of my loving wife. Nina and I met as graduate students, and she has always been a strong believer in me and a sharp editor of my manuscripts, grants, and talks.

How did you end up becoming a developmental biologist?

I ended up in a large, umbrella, graduate program at Duke, and I went into it thinking that I wanted to work on physiology. I didn't really know much about developmental biology, but I did a rotation with Dave McClay and was just taken under his spell.

He's this incredibly enthusiastic person who loves science and everyone in his laboratory. At that point, I fell in love with developmental biology. If you're interested in cell biology, then development is where everything happens really dynamically.

David Sherwood

It was interesting working on sea urchins. Because the field is small, you get to know the literature very quickly, and you get noticed when you do an experiment that gives a positive result. You feel like you're making an important contribution and that's incredibly empowering for a young scientist.

You're also forced to look beyond the boundaries of the field, which is very important. You go to developmental biology meetings and learn about zebrafish and *Xenopus*, about *C. elegans* and mouse. So I was in a great position to choose a postdoc laboratory and think of a good question to ask for my future career.

THE BREAKTHROUGH

Why did you choose to work on worms for your postdoc?

When I was in graduate school, there wasn't a single *C. elegans* researcher at Duke. I remember distinctly when Cori Bargmann came and gave a seminar on her olfaction work; I was in absolute awe at her system and its ability to understand a biological question at single cell resolution. I got that same experience over and over as *C. elegans* researchers came through. I was blown away by this model organism where you could really know which cell is signaling to which, and when.

When I interviewed in Paul Sternberg's laboratory, I felt a connection with him straightaway. Paul has so many diverse interests, from evolutionary biology, to cell signaling, to morphogenesis and behavior, that I thought it would be a spectacular place for someone like me, who loves all things biological, to spend five or six years.

Text and Interview by Ben Short
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I felt that he looked at science in a different way from me, that he was really nonlinear in his thinking and wasn't afraid of confusing results. If an experiment didn't work out, Paul would often say, "That's great—it's more complicated than we thought, and that means we have more to do."

I've been blessed in having mentors who are unflagging in their enthusiasm and support. There's nothing more important than having an advisor who's not only smart, but who will also say, "Hang in there, this is an important question; this is worthwhile." It's something I try to do in my own laboratory as well.

Of all the things you could have worked on, why choose anchor cell invasion?

When I first interviewed with Paul, I told him that I was interested in cell biology and morphogenesis. He said, "I've been thinking: the way that the uterus and vulva connect has got to be really cool because when you look at the EMs there are two basement membranes separating these tissues. Something has to happen to those membranes."

I discovered that at a very specific time, a single cell—the anchor cell—breaches both of those basement membranes and inserts into the underlying vulval cells. I remember the night I did the antibody staining, and saw a cookie-cutter gap where that anchor cell cuts through the basement membrane. I was screaming down the hallways; people thought I was crazy. But I knew, after two years in Paul's laboratory, that I had a great project because cell invasion is a fundamental process that has remained a mystery despite 30 years of study. You can't really recapitulate this complex behavior in vitro. You can't mimic the properties of an endogenous basement membrane or the extracellular signals that regulate the process.

Sherwood, aged 13 (right), fishing with his younger brother in Wyoming.

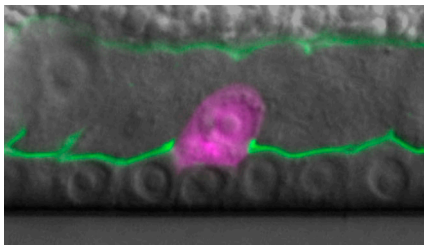
My first paper on anchor cell invasion remains my favorite because it was such a joy to not talk about a single gene, but to describe, for the first time, this beautiful model for cell invasion. It almost looks like a cartoon, and the genetics are spectacular because when you block anchor cell invasion, you get a protruded vulva and that's an incredibly easy phenotype to look for. And while *C. elegans* has always been a great system for genetics, the cell biology has lagged behind, particularly in post-embryonic development. Now we're using spinning-disk confocal microscopy to get better resolution of cell invasion in vivo than people are getting in vitro. We can do time-lapse imaging of anchor cells, which is key to understanding their invasion.

EXTENDING FURTHER

Is your system applicable to all types of cell invasion?

We don't know if everything we find is going to be generally applicable, and it's very likely that it won't be. The composition of basement membranes varies between tissues, so cells are likely to adopt different strategies. Nevertheless, we've already seen many parallels with what's thought to occur in vertebrates. For example, the first mutant that I isolated was in the transcription factor FOS-1, which is upregulated in a number of metastatic cancers, and is associated with invasive behavior in vitro.

When I was in Paul's laboratory, Jean Schwarzbauer sent me a GFP-tagged extracellular matrix molecule called SPARC; I wanted to use it as a basement membrane marker. I crossed SPARC-GFP into the FOS-1 mutant background and all of a sudden the anchor cells started to invade much better. Somehow, SPARC was suppressing the FOS-1 phenotype. It turns out SPARC is overexpressed in many different metastatic cancers, and we're starting to understand the mechanism by which it promotes cell invasion.



The anchor cell (magenta) breaches the basement membrane (green) to contact the underlying vulval cells.

We've also identified cofilin as having a beautiful invasion defect in an RNAi screen. When John Condeelis's group isolates cells from mouse breast tumors, one of the genes that's most upregulated and associated with metastatic potential is cofilin. So I think that what we're learning in anchor cells will have broad implications to understanding cell invasion in general.

Why did you choose to go back to Duke?

Duke has a perfect balance between quality of life and work. I love the biology department here because it has very eclectic interests, while the teaching really sharpens my intellect and broadens my understanding of biology.

We live five minutes away from Duke on this amazing property that backs up to Mud Creek along Duke Forest. It's a joy to live there; my sons are out on their bikes every night and they can wade in the swamp collecting frogs and tadpoles. Over the last several years, I've been rediscovering my hobbies. I play a lot of basketball; I play piano and sing with my boys. My wife is second generation Chinese and I'm finally learning the language. It's important to show your students and postdocs that you can invest a lot in this job and still have a great life.

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