People & Ideas

Matt Gibson: The blueprints of tissue architecture

Gibson studies the genetic and physical processes that help epithelia get in shape.

Epithelia come in all shapes and sizes. The cells themselves can be columnar, cuboidal, or squamous in shape, whereas the tissue as a whole can take up a variety of forms. *Drosophila* imaginal discs, for example, are flattened epithelial sacs that develop into different adult organs and appendages, such as the eye and wing.

Matt Gibson began his scientific career studying imaginal discs as a graduate student in Gerold Schubiger's laboratory at the University of Washington, Seattle. There, he investigated the extracellular signals that regulate the growth and patterning of these primordial tissues (1–3). Gibson continued his work on epithelial morphogenesis during postdoctoral research with Norbert Perrimon at Harvard Medical School. He uncovered an unexpected role for the BMP signaling pathway in controlling the shape, as well as fate, of epithelial cells depending on their position within imaginal discs (4). Gibson then led a second study explaining how the irregular "cobblestone" topology of proliferating epithelia arises in a predictable pattern as a direct result of cell division (5).

In 2006, Gibson began his own laboratory at the Stowers Institute in Kansas City, MO. He continues to study how proliferation and morphogenesis combine to form epithelia as diverse as a fly's wing and a sea anemone's tentacle. In a recent interview, Gibson described how his own career has taken shape.

LAYING THE FOUNDATIONS

What were your early science experiences?

Probably like a lot of biologists, I was interested in bugs and other small creatures as a kid. I used to keep all kinds of different animals in my room: snakes, fish, and salamanders. My mom would probably tell you about a spectacular slime mold I grew in my bedroom footlocker as a teenager. But then I had a really good biology teacher in high school, who did actual experiments with us. I remember doing one big project on planarian regeneration. That really turned me on to experimental science. The first biology course I took in college was Developmental Biology with Doug Kankel and Frank Ruddle at Yale; I was hooked from there and started working in laboratories. I think if it had only been about the textbook, I would never have gone forward with a science career.

What do you think you would be if you weren't a scientist?

It's hard to imagine at this point… maybe a park ranger. I like doing outdoor stuff—like mountain climbing and fly-fishing—whenever I get the chance, so I'd really want to do something outside. But anyone who works inside every day probably fantasizes about that. I really don't know what I would do; I'm not sure I could do anything else. I'd probably be living in my mom's basement or something!

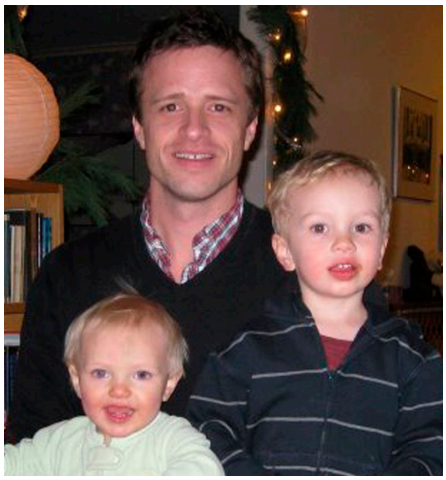
When did you first become interested in epithelial morphogenesis?

The first work I did with Gerold Schubiger in graduate school dealt with the regeneration of *Drosophila* imaginal discs. It became clear that it was necessary to understand tissue architecture in order to really put together what was happening in terms of signal transduction and pattern formation.

In that particular work, we were interested in imaginal disc columnar epithelia, but there's also this overlying squamous layer of cells called the peripodial epithelium. The peripodial cells are often neglected, but it turned out that they play a critical role in regeneration. That's what got me thinking about how different processes of signal transduction, pattern formation, and regulation of proliferation play out in the context of an epithelial layer.

Why did you choose Norbert Perrimon's laboratory for your postdoc?

It seemed like a good place to study the questions that interested me. In particular, David Bilder had come through that laboratory, and he had done some really interesting work on cell polarity and tumor suppressors in epithelia. I also knew that Norbert's postdocs got to define their own projects, and execute them in a pretty independent way. From a training standpoint, I felt ready for some degree of latitude in what I wanted to do.



Matt Gibson with his children.

BUILDING COLLABORATIONS

How did your postdoc projects evolve?

Initially, I wanted to study interkinetic nuclear migration—the movement of nuclei that is coordinated with the cell cycle in pseudo-stratified epithelia. I didn't wind up doing it, although I'm actually trying to make progress on it now! Instead, I started off more generally with a mosaic genetic screen for interesting defects in epithelial morphogenesis. From that came a mutation that produced rounded epithelial cysts, which extruded from the developing wing disc. The mutation causing this phenotype turned out to be in the BMP receptor *thickveins,* and we ultimately identified a role for BMP signaling in the control of the microtubule cytoskeleton and epithelial morphogenesis.

The next project, on epithelial topology, was funny because it really came out of my attempts to improve our capacity to do time-lapse experiments and follow imaginal disc development over longer periods. I spent hours and hours staring at the polygonal pattern of epithelial cells, until that pattern, in and of itself, started to become interesting. In most proliferating epithelia, there's a mix of cell shapes from quadrilaterals to ten-sided cells, but the distribution of these different shapes is not completely random.

I developed my own little theories about how this equilibrium topology is achieved, and

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tried to work out how cell division would affect topology, but I really didn't have the quantitative capacity to deal with the problem. So one day I Googled "Harvard," "morphogenesis," and "modeling," and the first name that came up was Radhika Nagpal in Harvard's department of Engineering and Applied Sciences. I immediately picked up the phone and called her, and there turned out to be a real convergence of interest on this particular problem.

How do you work with someone who has such a different area of expertise?

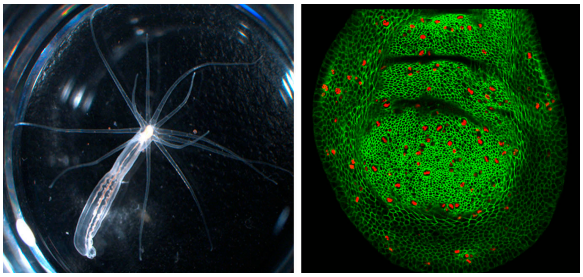
Collaborations work when two people with different skill sets can also communicate effectively. You need to have a common vision or understanding of what's going on. It really clicked with Radhika, and with her student, Ankit Patel. We understood the essential problem the same way. They were able to communicate their component of it, and they got from me what the biology was. We were able to speak a common language and put those pieces together. That was definitely a fun project; it really felt like I was doing something completely different than I'd done before.

Did it change your outlook on science?

I do think it changed my perspective. It's really interesting that the seemingly random activities of individual components, like cell divisions, can lead to the emergence of an ordered process or pattern, such as the equilibrium epithelial topology. Emergence is a fundamental concept of how biology works. Experimentally, however, it's very hard to directly demonstrate most of the time.

I've never had much interest—or proficiency—in biochemistry and the deepest levels of molecular mechanism. The kinds of questions that appeal to me are generally above the level of a single gene or protein. I view appendage development in the physical context of its three-dimensional tissue architecture rather than as a system of genes.

Typically, we knock out genes, see some defect, and ascribe the whole defect to the function of that one gene. But there are other ways that the system behaves which can't be dissected so easily; the effect of differential rates of cell proliferation on tissue architecture, for example. Physical processes are a bit of a black box in developmental biology. These are really interesting problems, but they require a certain kind of quantitative expertise. I just dance around the edge of them. Most of the current projects in my laboratory involve straightforward molecular genetics.



Gibson studies the morphogenesis of epithelia as diverse as sea anemone tentacles (left) and *Drosophila* wing discs (right).

AN ANCIENT BLUEPRINT

What are you working on currently?

We've got one project that follows up on how the BMP receptor *thickveins* maintains epithelial architecture. We did microarray analyses of cell clones that lack this receptor and looked at transcriptional differences with the surrounding tissue. We've identified new BMP targets, including a gene that seems to encode some kind of extracellular antagonist of the pathway. We've gone into a bit of detail on that particular molecule with the hope of better understanding the extracellular movement of the BMP morphogen in the developing wing disc epithelium.

We also have a few projects on mutations that affect either cell or tissue growth. We're interested in the interplay between growth and morphogenesis; how tissue growth affects tissue architecture.

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You've also started working with sea anemones…

When the *Nematostella* [sea anemone] genome came out, one of the amazing things was its similarity to the human genome. All the signaling pathways are there. And many human disease genes are actually present in the *Nematostella* genome, even though they're not present in flies. It made me realize that *Nematostella* is an ideal system to understand the ancient functions of all the molecular processes that we know and love in bilaterians.

There are some really good laboratories that work on the system, but they're mostly looking at very early embryogenesis. I'm interested in understanding both the regulation of growth in early-branching metazoans, as well as the specification and growth control of tentacle primordial in *Nematostella*. Over the last year, we've gotten our cultures going, and we've learned all the basics of husbandry. It's only in the past six months that we've attempted to do serious experiments.

We can exploit the fact that we're a fly laboratory to carry out experiments where we put *Nematostella* genes into flies, and assess whether they retain their function. We've got one story where we take a critical growth regulator and make a mutant form of it that's known to be hyperactive in flies and vertebrates. We see that the sea anemone gene induces overgrowth in transgenic flies, so it seems to have retained its function deep into the metazoan phylogeny, at least back to the common ancestor of cnidarians and bilaterians.

It sounds intriguing…

We'll see whether the project truly pays off, but it promises to give some very interesting answers about the evolutionary history of growth control. It's something that I couldn't have done, at this stage in my career, anywhere but the Stowers Institute; I probably wouldn't have gotten the funding to do it elsewhere. But this is a unique place where I felt encouraged to move in new directions and take these kinds of risks. The institute is very small, which makes it extremely collegial, and we have amazing core facility support, which has really helped to get things going. Overall, I couldn't be happier to have landed here.

1. Gibson, M.C., and G. Schubiger. 1999. *Development.* 126:1591–1599.
2. Gibson, M.C., and G. Schubiger. 2000. *Cell.* 103:343–350.
3. Gibson, M.C., et al. 2002. *Dev. Cell.* 3:451–460.
4. Gibson, M.C., and N. Perrimon. 2005. *Science.* 307:1785–1789.
5. Gibson, M.C., et al. 2006. *Nature.* 442:1038–1041.