People & Ideas

Didier Stainier: How function follows form

Stainier uses zebrafish as a model to study the cellular basis of organ development.

Organismal development is a time of dramatic movements and sweeping changes. Individual cells and entire tissues migrate, twist about, and adopt new fates as they move through a shifting milieu of chemical and physical signals.

These phenomena have long fascinated Didier Stainier. As a postdoc he participated in the first major forward genetic screens for mutations affecting zebrafish development (1). His work includes tracking the origins of cells as they form new organs (2), closely following how cells move during development (3), and studying what mechanisms contribute to these behaviors (4, 5). We called him to learn more about how the cellular dance of embryogenesis has led him through new steps in his career.

INTERNATIONAL COOPERATION

Did you have much exposure to science as a child?

My mother worked in the zoology department at the University of Liège back then, and I certainly spent a lot of time in the department's natural history museum. My paternal grandfather was also a professor at the university, in pharmacy, and my father went into pharmacy, too. So, biology and medicine were certainly present in my environment growing up.

But my parents felt that I was not very challenged academically by the schools in Liège, so I actually left Belgium when I was 15 and finished high school in the UK, at an International School in Wales. When I went there, I took physics, math, and biology, and I had a very good biology teacher. That really solidified my interest in the field.

What was special about this school?

It's actually part of an interesting movement called United World Colleges. It was founded after the Second World War by a group of people who wanted to promote international understanding through education. I had a roommate from Iran, one from Zambia, and another from Argentina, so it was an experience that opened up my world tremendously. I think, if I had not gone there, I would have probably stayed in Belgium for my entire life.

When you go to one of these schools, the idea is that you go back to your own country and promote the ideals of the movement. So, I went back home and entered the biology program at the university in Liège. But I was itching to do some lab work, and there were no undergraduate research opportunities there, so I went to Brandeis to finish my bachelor's degree.

At Brandeis I entered a lab right away and was essentially in the lab the whole time I was there—doing a lot of Southern blots and learning from my mistakes. That was exactly what I wanted to do. It was a great time, and, from there, I applied to graduate school.

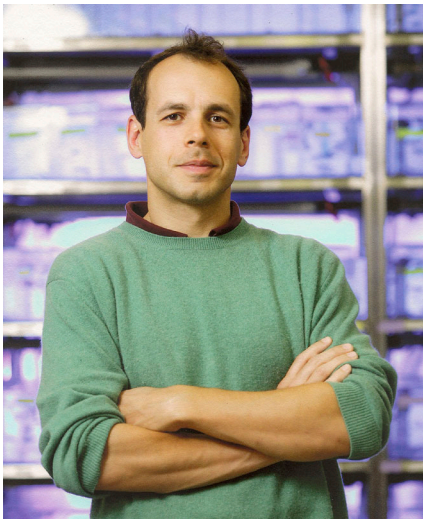
> "It was an experience that opened up my world tremendously."

FIRST MOVES

You joined Walter Gilbert's lab at Harvard…

Wally had just come back to Harvard after founding and leading Biogen, and he had this idea to make monoclonal antibodies against cell surface antigens in the mouse brain to look for axon guidance or cell–cell recognition molecules involved in the formation of neural circuits. I thought that was a pretty neat project, and I decided to join his lab.

Later, when I was looking for a postdoc, I was planning to stay in neuroscience. I met with Mark Fishman, who until that point had been mainly focused on neurobiology. But when we met, he told me that he had just gotten a large grant from Bristol-Myers Squibb to start a cardiovascular research center, and he'd just hired someone to study cardiovascular development in the chick.



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Didier Stainier

In Wally's lab, a psychiatry fellow had brought some zebrafish to the lab to work on. I don't know if you've ever looked at a zebrafish embryo, but one of the first things that jumps out at you is the heart and blood circulating through the organism. So I said to Mark, "Well, what about doing this in zebrafish?"

Mark had lots of money and was happy for me to give this a try, so I decided to join his lab. Then Mark hired Wolfgang Driever—who had been a graduate scientist with Janni Nüsslein-Volhard—as an assistant professor. Wolfgang and I both wanted to do forward genetics in the fish, so we decided to join forces to do a large-scale screen. There was an entire issue of *Development* where all these screen papers from Boston and Tübingen were published.

***One of the genes you studied as a postdoc was* cloche…**

cloche was actually one of the first mutants I studied. Even before we did the mutagenesis screen, I bought some wild-caught fish and started breeding them, and this mutant came out that had no blood vessels. Of course, we didn't know what the lesion was, and, in fact, we still don't know what the lesion is. The gene is located in one of the telomeres, so it's been really hard to identify. We're still working

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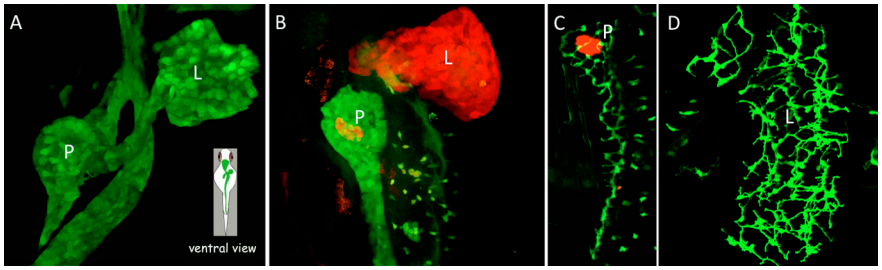

Forward genetic screens enabled study of liver (L) and pancreas (P) (panels A and B) and of intrapancreatic and intrahepatic ducts (panels C and D, respectively). In panel B, hepatocytes and pancreatic β cells are labeled red.

on it, and hopefully we'll figure it out before I have to retire. [Laughs]

Your work has touched on development of many different organs and tissues…

When I left Boston to go to the University of California, San Francisco (UCSF), there were a few mutants I was most interested in. In addition to *cloche*, there was a group of mutants that all showed the same "cardia bifida" phenotype where the animal forms two hearts, one on each side of the midline. By studying those mutants, we found transcription factors that regulate the formation of the endoderm, and we quickly became interested in endodermal organs.

As postdocs moved through my lab, I decided it would be easier for me to start working on a new organ than for them to do it, so I let many people take their projects with them when they left. Then my lab would start working on a new organ. This works for me because I like learning new things. Also, by bringing together people who are working on different organ systems in the zebrafish, there are a common set of techniques but less chance of scientific overlap, and a lot of synergy can take place. Of course, as we've spread out, we haven't been focused on going deeper into certain questions, but now we're starting to go back to address some of them.

ANOTHER MIGRATION

You've also studied cell migration in the early embryo…

One of the cardia bifida mutants that we were working on, called *casanova*, turned out to encode a transcription factor of the Sox family—Sox32. The neighboring gene, *sox17*, had long been studied for its role in endoderm formation, and one of the postdocs in my lab made a transgenic line using a *sox17* promoter to drive GFP expression. We could get very good resolution when imaging these cells.

This is where we were when Stephanie Woo came into the lab. She'd always been interested in cell migration and protrusive activities, and she wanted to look at the behavior of these early endodermal cells, so she made a utrophin-GFP line to label their actin cytoskeleton. Very interestingly, she saw that, at early gastrulation, endodermal cell migration appears random, but later on it is more directed and persistent. So, she looked at the transcriptome at various stages during the development of these cells to identify genes that might be involved in these different behaviors.

> "One of our big areas of focus now is to go beyond simple fluorescent protein reporters."

We knew from the work of a number of people that the TGF-β family member Nodal induces the formation of endodermal cells. But we wanted to test the hypothesis that Nodal was also modifying or modulating their migratory behavior. We showed that it does so at least in part by promoting the activation of the Rho GTPase Rac1 early in gastrulation.

At this point, we've established some of the tools we'll need to look at the migration of these cells with fairly high resolution and also to manipulate single cells. I think it will be interesting to test some of the models from others' in vitro work in an actual in vivo setting. One of our big areas of focus now is to go beyond simple fluorescent protein reporters. We want to be able to look at reporters that label intercellular organelles or tell us about the metabolic state of the cell or the localization of various important factors and to see how these correlate with cellular behavior. And of course, many of these same questions that we're asking with endodermal cells we'd also like to look at in the context of blood vessel formation or the development of other organs. There's a lot more to learn.

Will you be doing this work in zebrafish?

We're going to keep working with zebrafish and keep focusing on processes that we can image in the fish. But actually, about two years ago, I received an offer to move from UCSF to the Max Planck Institute in Bad Nauheim. I was trying to decide on this offer, and I asked my lab, a bit tongue-in-cheek, "If you had unlimited resources, what would you like to do?" Half the people said that they would like to do some mouse work.

I think part of the reason for that is that, if we find something interesting in fish, we'd like to know whether that gene or pathway has a similar function in mouse. The Max Planck Society is very generous when it comes to animal care, so now that my lab has almost completed the move here, we are branching out into mouse studies.

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