

## Carl-Philipp Heisenberg: Early embryos make a big move

Heisenberg is studying how cells' physical properties drive early developmental events.

**E**arly on, the embryo is basically a ball of undifferentiated cells. But at gastrulation, three new cell types (ectoderm, mesoderm, and endoderm) emerge and begin to organize into primitive structures, establishing the basic patterns upon which embryonic development will elaborate.

Carl-Philipp Heisenberg is fascinated by how these embryonic progenitors organize into separate tissue layers (1) and the mechanisms that drive this phenomenon. His work, at the interface between biology and physics (2–4), explains how the basic physical properties of these three cell types dictate their developmental destinies (5). We called him at his lab at the Institute for Science and Technology, a new multidisciplinary institute on the outskirts of Vienna, to hear about the movements of embryonic progenitor cells and the paths he has followed during his career.

### VALUABLE ADVICE

*You have some family background in the sciences...*

My grandfather was Werner Heisenberg, the quantum physicist, and that probably made science seem like a realistic career option in my family—not necessarily a natural scientist, but a scientist in general. But my uncle, who studies *Drosophila* in Würzburg, Germany, advised me that I should study biology and not physics, because there's more to find out in biology than in physics.

I must confess that early on I was not particularly interested in biology. I probably found it as interesting as many other things when I was young. It was when I joined my first lab, as a diploma student at the Max Planck Institute of Neurobiology near Munich, that I started thinking of becoming a biologist. I was looking at the function of different neurotrophic

factors in neurons of the rat cerebellum, and I found it fascinating to see, first of all, how little was known about the activity of these factors and, second, how much one could learn from doing experiments on them. I liked that you could be both creative and productive in thinking about scientific problems and their solutions.

### And your path was set from then on?

Actually, my original intention was to do my PhD in Cambridge at the Department of Anatomy and to continue working on neurotrophic factors. But then my supervisor left to join a company in the US, so I had to find another lab to do my PhD. I contacted my uncle again, and he suggested I think about working with zebrafish because there was

some exciting work being done with this new model organism. He advised me to approach a couple of different labs, and one of these was Christiane Nüsslein-Volhard's lab in Tübingen.

At that time, Janni was gearing up for a big mutagenesis screen in zebrafish—probably the first phenotypic screen for mutants in a vertebrate. I found the prospect of being part

of a large project, with so many people involved, to be very interesting.

### GRADUAL SHIFT

#### What was your role in this project?

My specific interest, at that time, was still looking at brain development in zebrafish. I think the main challenge at this time—besides screening phenotypes—was choosing interesting mutant phenotypes to continue working on. And instead of going for a very large phenotypic class with many mutants, I focused on two mutant phenotypes that I found particularly interesting and that had defects in forebrain development.



Carl-Philipp Heisenberg

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One mutant was called *masterblind*, and the other mutant was called *silberblick*. I started working on them in Janni's lab and continued when I moved on to Steve Wilson's lab in London for my postdoc. Both of them turned out to be very interesting genes, encoding members of the Wnt signaling pathway, but I became particularly interested in *silberblick*, which has a mutant phenotype much earlier in development, before the forebrain actually develops. It has phenotypes in gastrulation movements.

#### How well was gastrulation understood when you started working on it?

There was actually a very large body of work, some very sound and detailed studies, looking at this process in a descriptive manner. I think what was missing was that no one had yet employed high-end imaging and biophysical approaches to analyze and understand these phenomena. This is really what we started to contribute: developing various imaging and biophysics techniques to characterize mutant phenotypes and to understand what triggers cell segregation, sorting, tissue formation, and morphogenesis during gastrulation.

#### What happens to the embryo during gastrulation?

When ectoderm, mesoderm, and endoderm cells arise, the embryo has to segregate them into three different layers of cells, with the ectoderm on the outside,

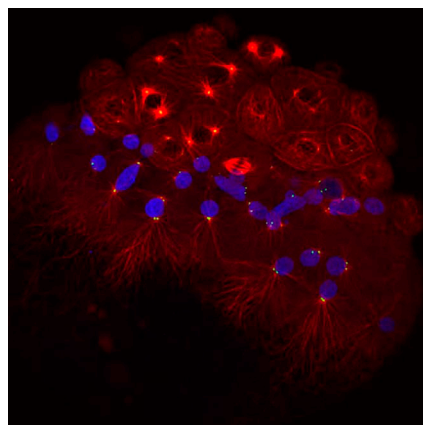
**"No one had yet employed high-end imaging and biophysical approaches to analyze... these phenomena."**

the endoderm on the inside, and the mesoderm in between. This is what gastrulation is really about. It's a process of cell segregation and layer and boundary formation between the different cell layers. These events might sound very simple, but they are actually very complex at a mechanistic level.

#### *What drives this process?*

One property of these cells that is particularly important is their adhesiveness. When we started to think about adhesion, we were pretty naïve, and we thought of adhesion as being equal to the amount of adhesion molecules expressed in a given cell type. However, we soon realized that the expression of cadherin adhesion molecules, which mediate adhesion between progenitor cells, did not match with their segregation behavior. So, when I started my own group at the Max Planck Institute of Molecular Cell Biology and Genetics in Dresden, we first developed a number of techniques to try to measure cell adhesion by looking at the amount of force needed to separate two adhering cells.

It surprised us to find that the amount of cadherins at a cell–cell contact has very little predictive value for the strength and the size of the contact. What is really important is how adhesion molecules signal to and modulate the cell cortex at the contact site. This is what determines how big the contact becomes and how strong it is.



A zebrafish embryo at the onset of gastrulation (with microtubules shown in red, nuclei in blue, and centrosomes in green).

#### **BIG MOVES**

##### *How does that affect the large-scale reorganizations observed at gastrulation?*

Differentiation of mesoderm and endoderm is induced during gastrulation by Nodal/TGF- $\beta$  signals. These Nodal signals directly affect cortical tension of mesoderm/endoderm cells, making them softer. This is important because what determines the contact size between two cells is the difference in cortical tension at the contact versus outside of the contact. Ectoderm cells are able to form large contacts with each other because they can strongly reduce their cortical tension at sites of cell–cell contact, whereas mesoderm and endoderm cells aren't able to modify their cortical tension as much as ectoderm cells can and thus form smaller cell–cell contacts.

This is a key feature that drives the segregation of ectoderm from mesoderm and endoderm. In fact, if we mix these different cell types together in culture, we see that they segregate in specific spatial configurations: the ectoderm cells end up in the middle because they are most cohesive and form the largest cell–cell contacts. They're surrounded by mesoderm and endoderm cells, which are less cohesive and form considerably smaller cell–cell contacts. This is actually a phenomenon that has been observed for many, many years and goes back to very early experiments.

##### *That's inside-out compared to a real embryo...*

That's absolutely right, and the reason is that there are other interfaces in the embryo, such as the interface with the yolk cell or the surface epithelium, which will mostly likely modify the sorting order of these cells in the embryo.

##### *Is cadherin differently active in the different progenitor cell types?*

That's one thing we're looking at right now. Our working hypothesis is that the



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Heisenberg and his wife keep a close watch on another developmental process.

basic difference between the different progenitor cell types is their cortical contractility. The cortical contractility acts on these adhesion molecules, and it induces (via the mechanosensitivity of these cadherin adhesion sites) changes in the architecture of these adhesion sites, which, again, changes their mechanical coupling function and their signaling function.

There's some sort of mechanosensitive feedback loop operating here, and we would like to understand better how this works.

Mechanosensitive feedback processes are something I find very interesting, and they might be operating in some of the other developmental processes we study in the lab. We are also interested in how adhesion controls cell division

orientation and how cell divisions affect tissue morphogenesis. There are many interfaces of adhesion, and these are just a few of the directions that we would like to go in the future.

**"The basic difference between the different progenitor cell types is their cortical contractility."**

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