Isabelle Vernos: Motoring around the mitotic spindle

Vernos uses cutting-edge microscopy to track spindle assembly in *Xenopus* eggs.

The construction of the mitotic spindle must be tightly orchestrated to ensure the proper distribution of a cell's chromosomes to the next generation of cells. Chromosomes are put through their paces in this complicated dance by the coordinated action of several specialized microtubule motor proteins, some of which reside directly on chromosome arms.

Isabelle Vernos has a long-standing interest in the highly organized processes that give rise to new daughter cells. In her postdoctoral work, she sought out microtubule-associated proteins (MAPs) in *Xenopus* oocytes, which led to the discovery of many kinesin-related microtubule motors (1). Ever since, Vernos has probed the functions of these motors (2) and the proteins that regulate their activity as they organize the mitotic spindle (3, 4).

Now ensconced in her new lab at the Center for Genomic Regulation (CRG) in Barcelona, Spain, Vernos is following that theme from the metaphase plate to the centrosome (5). We asked her how molecular motors have taken her on a tour of spindle biology.

TAKEOFF

When you were a graduate student studying fly development, some of your flies were astronauts, weren't they?

[laughs] Yes, that's true! That was really more of a side project for me, studying the effects of microgravity on the development of the *Drosophila* embryo. At the time, I was very interested in development, and especially pattern formation. I really liked the idea of trying to understand how you can obtain a full organism from a single cell. There was—and still is—a very strong school of geneticists in Madrid, and I became involved in a collaboration between Ginés Morata's and Roberto Marco's groups, studying the bithorax complex in *Drosophila* as my main research focus.

The microgravity project was Marco's. Part of the reason I got involved was because I could speak English—which was not so common in Spain at the time—so I could serve as liaison with the people who were actually planning the mission. We spent a lot of time thinking about how we could manage having flies aboard the Shuttle. The group ended up designing these special boxes for the animals, which had all these layers of security to prevent the flies from escaping. Then we had to work out how to recover the embryos to study them, and what kinds of experiments could be performed on them. Once that was all settled, we got to interact with the astronauts and teach them how to handle the boxes, which was fun.

> "We got to interact with the astronauts and teach them how to handle the boxes."

As a postdoc with Chris Wylie at the University of Cambridge, why did your interests shift to motor proteins in* Xenopus*?

It's not actually as big a departure as it may seem. At the time, I was very curious about the specific localization of mRNAs and proteins in very early oocytes and embryos. I wanted to understand how this could happen. It was clear at the time that the cytoskeleton—in particular, the microtubule cytoskeleton—was involved in the process. I began to be interested in microtubules and microtubule-associated proteins, or MAPs. Very little was known about MAPs then, except for some work that had been done on brain MAPs. I wanted to move into a different experimental system, so I proposed a project to try to identify MAPs in the *Xenopus* egg.

MEET AT THE MIDDLE

There are lots of motors in* Xenopus *eggs, aren't there?

There are two types of microtubule motors in cells: kinesin and dynein. Soon after starting my postdoc, some papers were published identifying novel proteins in *Aspergillus* and in the fly containing a domain highly similar to the kinesin motor domain. So, we went about trying to see whether there were similar proteins in *Xenopus*. That was a very intense time for me. We were using degenerate PCR primers to pull out new genes and I was doing all the sequencing myself, but at that time I also had two children, so I had to be very organized about getting both science and parenting done. It was difficult, but you can get a surprising amount of work done if you're well organized. We ended up finding many more motors than we had expected to find. I don't think anyone thought there could be so many.

Isabelle Vernos

You had a bounty on your hands—did you have an idea where this would take you?

The science was going very well, and it was around that time that my husband, Luis Serrano, was invited to be a group leader at the EMBL in Heidelberg, Germany. When I told my friends we were

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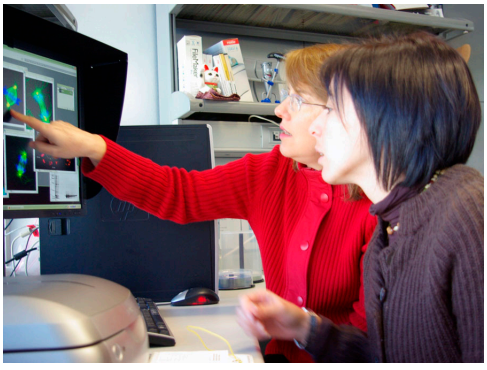
moving to EMBL, they all said, "Oh, you have to speak to Eric Karsenti." I did, and I took a postdoc position in his lab, which ended up being the perfect thing for me. I think it was still my dream to find a model system in which to study the localization of early developmental determinants. But Eric said to me one day, "You know, maybe your kinesins are involved in cell division."

I looked at him and said, "Oh no, I don't think so." But in the end, he was right. We set up a system to look at mitotic spindle assembly in cell extracts, and that was when things started getting really interesting. At the time, the prevailing idea was that the centrosomes were the main organizers of the mitotic spindle. But Eric had this long-standing idea that chromosomes or chromatin are important for controlling spindle assembly. Meanwhile, I had found that these *Xenopus* kinesin-like proteins were present on the chromosome arms. Xkid and Xklp1 were the first motors that I really characterized. We came up with the idea that they were involved in creating the "polar ejection force" that helps position chromosomes at the metaphase plate. But they contribute to other aspects of spindle assembly as well.

Ultimately, there are lots of different motors playing different roles in mitosis. Some of these are really organizing microtubules, interacting with them directly and perhaps regulating their dynamic properties. There's also a specific set of motor proteins that associate with the chromosomes: you find some of these at the kinetochore, but others are on the chromosome arms.



Vernos and colleague discuss spindle biology.

PLANNED ITINERARY

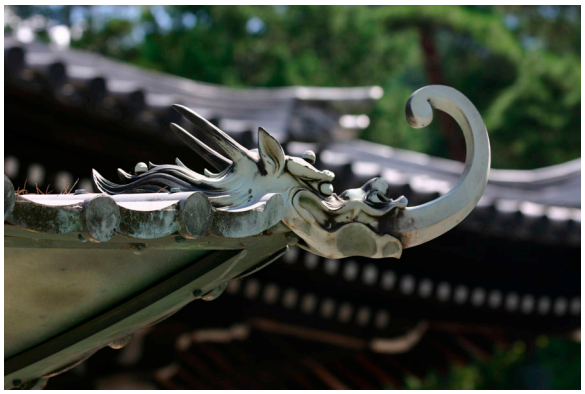
Your lab has also started working on non-motor proteins as well?

Yes, in fact we wanted to understand how the motor Xklp2—that we had previously found to be plus end directed—was targeted to microtubule minus ends. When I was a staff scientist in Eric's lab, I co-supervised the PhD work of Torsten Wittmann, who identified Tpx2 as the protein targeting Xklp2 to microtubules. But Tpx2 later turned out to also be an important factor in the Ran-GTP pathway that controls the nucleation and assembly of microtubules along the chromosome, independently of the centrosome. That led us to explore how this Ran-GTP pathway functions, and which other non-motor proteins control microtubule nucleation and assembly, and organize cell division.

Why did you move back to Spain after leaving EMBL?

It was a tough decision for us because Luis had also received an offer to head up a Max Planck Institute in Munich. But, I had spent part of my childhood in Spain, and I wanted to settle down here eventually, so when I got invited to be part of CRG, we decided to come here. Fortunately, he's happy here, where he's Director of the Systems Biology program.

Mine was one of the first groups in the Cell and Developmental Biology program at the Institute. So I've been heavily involved in helping set up the program and in developing the light microscopy facility here. That was a lot of work, but now it's up and running, and I'm able to focus on other things again.



Vernos has an eye for detail in photography as well as science.

> "I don't think anyone thought there could be so many motors in *Xenopus*."

What will you be working on?

I would really like to understand how the Ran-GTP pathway functions, and how Tpx2 works through the Ran-GTP pathway to trigger microtubule nucleation de novo, without a centrosome. This of course also makes me very interested in the centrosome, and in trying to determine the parallels and differences between centrosomal and acentrosomal pathways for spindle formation. We know the two pathways share common components, but the kinetics are very different. There is so much to do, sometimes I'm not sure where to start!

And then, too, it will be nice to be able to spend a little time outside of work with my hobbies: reading and photography.

What do you like to read?

Oh, everything, but if you had to pin me down to specific genres, I'd say autobiographies and science fiction. I don't know… I just love to read.

1. Vernos, I., et al. 1993. *Dev. Biol.* 157:232–239.
2. Antonio, C., et al. 2000. *Cell.* 102:425–435.
3. Gruss, O.J., and I. Vernos. 2004. *J. Cell Biol.* 166:949–955.
4. Vernos, I., and E. Karsenti. 2001. *Science.* 294:543–547.
5. Sardon, T., et al. 2008. *EMBO J.* 27:2567–2579.