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PEOPLE & IDEAS

Elvan Böke: Long live the oocyte

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Elvan Böke investigates the mechanisms that preserve the viability of dormant oocytes.

The clock is ticking. Decline in oocyte quality with age is a risk factor for female infertility. But what causes such a decline is still sort of a mystery science hasn't revealed... yet. The Turkish scientist Elvan Böke believes the metabolic and proteostasis machineries are crucial for oocytes to escape the passage of time. Throughout the years, she has witnessed how several of her friends and colleagues have gone through rather chaotic experiences with fertility interventions. "Their doctors did not have a scientific explanation for why one treatment worked while others failed or why one suggested treatment might work better than other possibilities," Elvan says. Since 2017, she has led the Oocyte Biology and Cellular Dormancy lab at the Center for Genomic Regulation (CRG) in Barcelona, Spain, that works toward understanding how oocytes can remain healthy from birth to the end of a woman's reproductive lifespan and why they eventually deteriorate with advanced maternal age. We chatted with Elvan to learn more about her scientific journey and future endeavors.

Elvan, let's travel back in time, almost at the birth of an oocyte. Did you always want to be a scientist?

Since I can remember! When I was a child, I was obsessed with the Teenage Mutant Ninja Turtles and Spider-Man—I had all their toys and t-shirts [laughs]. In primary school, I used to say that I wanted to become a geneticist to understand how genes mutated by radiation could give superpowers to my favorite TV cartoons. I was also fascinated with electroscopes. My mother is a physicist and, from time to time, brought me with her to the teaching physics lab at the high school where she taught. The swing of the electroscope needle with electrostatistical force somehow fascinated me.

Did you consider studying physics?

I was actually strongest in physics and math in high school! But being honest, I had always been more attracted to genetics, probably because of Ninja Turtles and Spidey. I studied molecular biology and genetics at the Middle East Technical University in Ankara, Turkey—a five-hour drive from my home city, Mersin. During my undergrad, I did a summer internship in the lab of Xandra Breakefield at the Massachusetts General Hospital, Boston. There I worked on the effect of microRNA-200a on the growth of meningiomas and schwannomas, where I co-authored my first paper (Saydam et al., 2009).

Where and with whom did you do your PhD and postdoc?

I did a 4-yr PhD at the Cancer Research UK-Manchester Institute in Manchester, UK, in the lab of Iain Hagan. I studied the cell cycle, working with fission yeast. I discovered that two major protein phosphatases in the cell, PP1 and PP2A, act in a relay to coordinate mitotic progression and promote mitotic exit (Grallert et al., 2015). This work was a breakthrough in part because it introduced a new, less kinase-centric view of mitosis. After defending my thesis in 2012, I took a few months off traveling in South Africa before I started my postdoc with Tim Mitchison at the Harvard Medical School, Boston. There, I worked with female germ cells for the first time.

Elvan Böke. Photo courtesy of the CRG.

Was it back then when your interest in oocytes started?

Yes, you could say so. In the Mitchison lab I discovered that *Xenopus* oocytes utilize a physiological amyloid cage to keep the Balbiani body—a non-membrane-bound compartment packed with mitochondria, ER, Golgi, and RNA—in a dormant state during their long resting period (Boke et al., 2016). My work was among the first descriptions of cells using amyloid-like assembly mechanisms to organize membraneless organelles. We also proposed that these tightly packed amyloid-like structures could prevent the diffusion of small toxic intermediates that could damage the cell. Oocytes are some of the longest-lived cells in the body—they form before birth!—and yet they retain the unique capacity to give rise to a new organism. Essentially, an embryo

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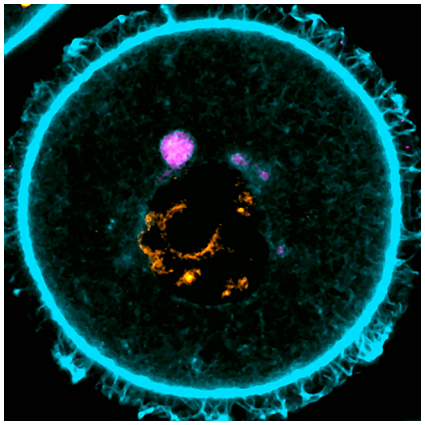

Mouse oocyte with actin labeled in cyan, DNA labeled in orange, and lysosomes labeled in pink. Courtesy of Gabriele Zaffagnini, a member of the Böke lab working on proteostasis in mouse oocytes.

must inherit all of its cytoplasm from a single cell that is 20–40 yr old! So, investigating the mechanisms that enable this feat of longevity was certainly a fascinating task I wanted to involve myself in and, thus, I decided to search for independent positions.

How was your faculty recruitment process?

I applied for faculty positions without my postdoc paper being published, and yet I was offered my top choice, a group leader position at the CRG. And the same happened to me before when I applied for a postdoc job in the Mitchison lab. Both my PhD and postdoc papers got published more than 6 mo after I received the prospective offers. I feel strongly that people should not wait for their papers to be "out" to start applying for jobs. If their research ideas are interesting and stand out from the crowd, candidates do stand a significant chance even without accepted papers.

What are you currently working on?

Poor oocyte quality accounts for most female fertility problems. However, we know little about how oocytes can remain healthy for many years or why their health eventually declines with advanced age. Worldwide data show that more than 25% of female fertility problems are unexplained, pointing to a huge gap in our understanding of female reproduction. Our lab is currently working to help fill this gap by studying the cell biology of immature oocytes. We are interested in three main lines of research: the metabolic state of dormant oocytes, the establishment of proteostasis in oocytes, and the susceptibility of dormant oocytes to aging. We have recently discovered that mitochondria keep a low but active metabolism in oocytes by limiting reactive oxygen species through removing complex I from the respiratory chain (Rodríguez-Nuevo et al., 2022).

What kind of approach do you bring to your work?

I am enthusiastic about what we are doing, and I believe in its impact on society. Several of my friends and colleagues who have gone through some sort of fertility treatment to conceive have received only vague responses from doctors as an explanation of why their interventions failed. I think part of the problem here arises because our understanding of female reproduction is very limited compared to that of many other fields of similar clinical importance. So, I guess my approach is to bring a lot of enthusiasm to my research, and I would like to think this influences our lab culture. We are a friendly and hardworking team—my lab members aptly named our lab's WhatsApp group "Work hard, play hard," and so far, I believe we have lived up to this classic motto.

Work hard as in collecting scarce and precious oocytes?

That's right. Sample collection is an extra effort for anyone working with oocytes. Literally, every experiment we perform begins by isolating ovaries from animals and then isolating oocytes from the ovaries. We can comfort ourselves by saying we work with physiological cells that matter—which is true—but still, I envy people who can just grow their cells in plates, or in culture flasks! Also, having access to human samples is hard. I was lucky that, when I started my lab, the Science and Technology Office of the CRG provided crucial assistance, introducing me to several in vitro fertilization clinics and hospitals that we have ongoing collaborations with, such as the Hospital Clinic Barcelona—the reference hospital in Catalonia for gynecological surgeries—to receive human ovaries.

What did you learn during your PhD and postdoc that helped prepare you for being a group leader?

During my PhD, I worked with yeast, a model system that allows researchers to test several hypotheses in relatively short timeframes. In yeast I learned how to test a research question and how to react when your favorite hypothesis fails—several times in a row! Indeed, I changed my main research project in the third year of a European 4-yr PhD program, and nevertheless I ended up making a big discovery for the mitosis field. In this way, my PhD helped me trust my own ideas and appreciate the value of a "successful" failure—a failure that leads you to a place where you can regroup and come up with a better plan.

My postdoc with Tim Mitchison was in many ways an introductory course on how to become a PI (principal investigator). As a postdoc, I could be in charge of my project, come up with my own ideas, establish collaborations, supervise students, write my papers, etc. This level of independence truly prepared me to run an independent group. Tim has been a huge but unassuming influence for me—we probably had fewer than a handful of one-to-one meetings throughout my postdoc, but simply being around him taught me a lot. His lab is structured such that it focuses on several independent problems with an overarching common theme—I inherited this "independent-projects-per-person-but-a-common-goal-for-the-lab" approach from him.

Any other influences in your career?

Oh, yes, Tony Hyman and Julia P. Cooper! I love that the Hyman lab has shifted focus a few times while remaining at the forefront of their fields—their latest tack involved opening the field of phase separation in biology. I appreciate the way Tony concentrates on the big picture but also has a sharp focus when needed to figure out important details. Julie Cooper was also kind of a role model for me while I was doing my PhD, though I doubt she is aware of this! Julie was in the UK at the time, and during my PhD I happened to listen to several of her talks. She is a great scientist—but also, I appreciated her very colorful slide backgrounds, her striking and fashionable attire, and her bubbly conversational style. I loved all these!

Now, if you could change just one thing in academia, what would it be?

Ahhh... If I could, I would change the academic promotion system. Many things that are essential for academia are not evaluated for promotions. How well are students

The Böke lab learning how to make paella in the 2021 lab retreat. Photo courtesy of Elvan Böke.

educated? How do the postdocs perform after leaving the lab? What did the lab really "discover" as opposed to where did they publish? I'm afraid none of these things will improve in the short term, though.

If you could rewind to your first day as a PI, would you change anything?

I would start advertising for positions in my lab sooner. My first students joined the lab 8 mo after I started, and my first postdocs could not join for 1.5 yr!

Any tips for a successful research career?

I encourage everyone to seek mentors whom they look up to scientifically, get along well with socially, and—this is crucial—with whom they do not work directly. Fresh perspective provided by my mentors at several critical moments has helped me enormously, especially during transition periods—i.e., from PhD to postdoc and from postdoc to PI.

And any good advice you have been given?

The mock-Latin motto "Illegitimis non carborundum" [often translated as "Don't let the bastards grind you down"].

I like the advice. Have you ever put it into practice?

Let me think... more like a version of that: Don't let the adversities grind you down. I have had to forge a career that started in a Turkish city [Mersin] you've never heard of, near the Syrian-Turkish border, overcoming many challenges that finally led me to where I am today. I moved to Ankara, Turkey, for university, to Manchester, UK, for my PhD, and to Boston, U.S., for my postdoc. To succeed from such beginnings, there is little room for error. One has to be at the top of the group at each stage—high school, university, PhD—and furthermore be lucky enough to find supportive mentors at each step of the way. As an example of the sorts of difficulties "international" students encounter: Nationality requirements in the UK meant that in Manchester I couldn't obtain an extension to write my PhD paper even though the very same extension was given to all other EU-resident students in my year who needed it... so, I have had to build some resilience.

Also, I have put into practice a most cheerful version of the saying: Don't let a teeny-tiny spot in a super-tight marina in Palamós, Catalonia, prevent you from parking a 35-foot sailboat [laughs].

Wait, what? I can't finish this interview without knowing if you own a 35-foot sailboat...

I wish; I love sailing! I have a skipper's license, and I try to rent a sailboat and sail somewhere every year with my husband. Our biggest adventure was sailing around the Society Islands in the South Pacific in 2019. I have to say that we may struggle to go back to sailing with a 10-mo-old baby these days—but hopefully sometime soon!

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