

CELL SCIENTISTS TO WATCH

Cell scientist to watch – Lena Pernas

Lena Pernas studied biology at the University of California, Los Angeles, USA and was a MARC Undergraduate Fellow with Kent Hill. For her PhD, she joined the lab of John Boothroyd at Stanford University, where she identified a *Toxoplasma* effector protein that tethers mitochondria and impacts the host immune response. Lena then moved to Italy to join Luca Scorrano's group at the University of Padua, funded by Life Science Research Foundation and EMBO postdoctoral fellowships. There, she discovered that host mitochondria restrict the growth of the human parasite *Toxoplasma* through nutrient competition. Since 2019, Lena has led a lab at the Max Planck Institute for the Biology of Ageing in Cologne, Germany, studying the organelle and metabolic dynamics of the host–pathogen interaction. Lena is a recipient of an ERC Starting Grant, a finalist for the 2022 Eppendorf Young Investigator Award, and the winner of the 2022 BINDER Innovation Prize.

What inspired you to become a scientist?

When I was younger, my father used to get us anything he could to inspire us, including scientific games and chemistry kits. Once he bought us a computer game called the Amazon Trail, in which if you contracted malaria as you were going through the Amazon, you had to find the *Cinchona* tree which yields quinine, a treatment against malaria. This really piqued my interest in infectious diseases, but I didn't really know how you could study them until my undergraduate studies at UCLA. The university was supported by the Maximising Access to Research Careers (MARC) training programme, which funds undergraduates to do research. As a MARC fellow, I started working on trypanosomes, the causal agents of the 'sleeping sickness' disease. I became fascinated by how these tiny organisms manipulate their hosts in such profound ways. Later during my undergraduate studies, one of my microbiology professors, Dr Patricia Johnson, encouraged me to be a course assistant for the 'Biology of Parasitism' course at MBL, where I got to listen to many more talks on the topic, and this is when I knew that parasitology is what I wanted to do.

It seems that you've also become a cell biologist as much as a parasitologist, with mitochondrial biology and metabolism being a key focus of your research

Indeed, and the irony of this is that during that undergraduate programme, when attending a journal club in which one of the students was discussing a paper on mitochondria, I remember thinking how boring these things are – they are not even real microbes! But now they have become my other obsession.

Having studied the relationship between *Toxoplasma* infection and mitochondrial biology for a larger part of your career, could you give a brief overview of the main findings of your research?

One of our key findings was that after the parasite invades the cell, mitochondria are able to restrict the parasite's access to



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fatty acids through nutrient competition by simply increasing their own fatty acid uptake. So this serves as a host defence, and opens up a lot of questions, including how mitochondria sense parasites. We've also discovered that parasites have an effector protein, MAF1, which staples the mitochondria to the parasite vacuole and leads to their fragmentation at late stages of infection. This led us to think that MAF1 might be doing something to the mitochondria to cripple the nutritional defence. Indeed, most recently we found that the mitofusins 1 and 2, which are required for the mitochondrial nutritional defence, end up shed on the outer mitochondrial membrane in structures that we called SPOTs, and are subsequently degraded. MAF1 binds a mitochondrial receptor, and so likely mimics a mitochondrial preprotein. However, because MAF1 is inserted in the parasite vacuole membrane, when mitochondria try to 'import' MAF1, they can't do so and instead trigger a cellular response to mitochondrial stress that leads to the shedding of the outer mitochondrial membrane. We think this all points to a host–pathogen arms race that is derived from mitochondria–microbe nutrient competition.

In this arms race, how can you determine whether the changes you see upon infection are a virulence or host defence mechanism?

This is a 'chicken or egg' question. In our SPOTs study, two key results suggest that mitochondrial membrane shedding is beneficial for the parasite – the parasite effector binding to the host receptor induces the formation of SPOTs that promote the

Lena Pernas's contact details: Max Planck Institute for Biology of Ageing, Joseph-Stelzmann-Str. 9b, 50931 Cologne, Germany.
E-mail: Lena.Pernas@age.mpg.de



Lena with her group on a recent lab retreat with other Scorrano lab alumni in Padua, Italy.

degradation of proteins required for nutrient competition, and in the absence of the receptor, the parasites grow slower. In preliminary work we've also seen that after mitochondria have shed their membrane, they take up less fatty acids. However, these findings don't exclude the possibility that mitochondrial shedding could be beneficial for the host in some contexts – for example, there are several microbial effector proteins that target the mitochondria, so you could imagine a scenario where this could be beneficial for the host cell by enabling it to shed bits of compromised membrane, or shed membrane that acts as a decoy to sequester microbial effectors.

“[...] I'm really excited about trying to understand how we can exploit metabolism to help combat infection.”

You've challenged the previous thinking of organelles being merely hijacked by pathogens with the nutrient competition concept. How was this received in the field?

I would say that it was met with both a healthy dose of skepticism and an 'of course, that makes sense'-type of reaction, since mitochondria are domesticated microbes and therefore it's perhaps not so surprising that they have competing metabolic interests with invading microbes. Where I usually get a lot of pushback is whether this has any relevance *in vivo*, so that's what we're trying to study now. Recent work from the group of Miguel Soares at the Gulbenkian Institute has shown that mice infected with malaria induce hypoglycemia to starve the parasites, so I think the concept that metabolism can be rewired as a defence mechanism is very interesting and worth further investigating.

Are you also exploring applied or therapeutic angles in your research?

Yes, I'm really excited about trying to understand how we can exploit metabolism to help combat infection. We would like to test if any of the defences we've uncovered *in vivo* can be used to treat human disease or to complement current treatments to microbial infections. For example, we've teamed up with the Max Planck Lead Discovery Center to identify enhancers of mitochondrial

health that have antimicrobial potential. We've also become interested in what *Toxoplasma* does to the approximately one-third of the human population that it chronically infects. During my PhD, in a collaboration with Dr Jose Montoya at the Palo Alto Medical Foundation, we found that patients infected with *Toxoplasma* who appear asymptomatic actually have basal differences in cytokine levels. This motivated work during the pandemic led by my former postdoc, Sara Beros, to ask what happens when patients with chronic infections acquire a secondary infection, and whether differences in COVID-19 severity could also be related to the presence of chronic *Toxoplasma* or herpesvirus infections.

Looking back at the time when you started your lab, what did you feel was the biggest challenge?

I would say that the biggest challenge was starting with a completely empty lab. It was a bit daunting to think about all the stuff I needed to order – and I wished there was a PI starter kit that you could just click and order [smiles]. It was also difficult starting a lab in a country in which you don't speak the language – I'm still trying to learn it, but German is a beast! There's a lot of bureaucracy when you are working with an S2 organism like *Toxoplasma*, but the folks at our institute were extremely supportive and helped me take care of such things.

What advice would you give someone seeking to become a PI?

Just go for it! Even if you receive a rejection, look at the bright side – you've put together an application, thought about your ideas and practiced your writing. It's also good to remember that nobody is that special, so if many of your peers can make it in academia, you can do it, too!

What is your approach to mentoring and establishing a good lab culture?

I'm really fortunate that I'm not bogged down by administrative or teaching duties, so I can focus my efforts on my lab. I try to adapt my mentoring style to all of my trainees, because every person is unique and therefore one strategy does not fit all, and to be available as much as possible. I still work at the bench, and I feel this helps me better advise my trainees on troubleshooting and experimental approaches. I also try to actively build a lab community by engaging lab members in different activities outside of the lab – for example, we've done a rock climbing excursion and participated in a 5 and 10 km running race.

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Is there any piece of scientific advice that has stuck with you or that you found particularly useful?

My PhD advisor, John Boothroyd, used to always tell us to talk to people and be open, because you never know what conversation or statement from someone can change your life. I think it's also important to talk about experiments because you learn so much more by discussing the intricacies and nuances of an experimental workflow with someone than by just reading the protocol. And then Luca Scorrano, my postdoc advisor, would

always say ‘Lena, don’t be married to your ideas’. This might seem obvious, but sometimes we can become so obsessed with our hypotheses that it becomes hard to analyse data in an unbiased manner – and of course it’s crucial to be agnostic when doing so. What helps me sometimes is to go back to the data months after the experiment, when I might have forgotten what our key hypothesis was.

If you could change one thing in academic research culture overnight, what would that be?

I wish there were more feedback systems in place. Trainees are often uncomfortable giving feedback to their supervisors, but I always encourage them to do so – otherwise how can I get better at what I’m doing? Also, for example when submitting grants, you sometimes get feedback, but more often you don’t – and especially when your

grant is not funded, it would be useful to know how you can improve next time.

Finally, could you tell us an interesting fact about yourself that people wouldn’t know by looking at your CV?

I’m a crossword puzzle aficionado, and whenever I have a free moment, I try to solve one. I think crossword puzzles are also a metaphor for so many things in life including projects – sometimes you can be on the right track and sailing is smooth, but if you make one small misstep, you can go down a rabbit hole and it will take you time to go back and figure out where the misstep occurred.

Lena Pernas was interviewed by Máté Pálffy, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewee.