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**Spotlight**

# Working together to fighting the bad guys

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Tackling one of the world's leading death-causing bacteria is a challenge Sabine Ehrt is ready to take on—and she has a whole team with her.

## Collaborating for optimal conditions

When Sabine Ehrt first got into contact with bacteria in University lectures, she almost disregarded them as being too simple. But soon she realised that 'they are actually not that simple; they are quite complicated, adapting to different environments, niches, and hosts.' After finishing her Ph.D. on adaptation strategies of *Acinetobacter calcoaceticus* at the University of Erlangen in Germany, Sabine switched to human pathogens for her postdoc positions at Cornell University Medical College in New York and the University of California at Berkeley. She took the chance to work on bacteria that require a biosafety 3 lab set up and deep dived into the question of how the death-causing pathogen *Mycobacterium tuberculosis* adapts to humans.

As an Assistant Professor in the Department of Microbiology and Immunology at Weill Medical College of Cornell University, Sabine started a substantial collaboration with Dirk Schnappinger to investigate the pathogen's adaptation mechanisms. *Mycobacterium tuberculosis* comes into contact with a host via inhalation and infects macrophages in the lung. Within the macrophage cytosol, the pathogen resides within phagosomes, but prevents them from fusing with lysosomes and thereby from clearing the pathogen. To investigate how the pathogen adjusts to the macrophage environment and how macrophages respond to the infection, Sabine and her team set up two major studies 'that used microarray techniques for the first time in tuberculosis research'. They found that *M. tuberculosis* senses the intraphagosomal environment through the presence of fatty acids and low pH. Hence, the pathogen responds by inducing anaerobic respiration, degradation of fatty acids, remodelling of its cell envelope and by producing siderophores for efficient iron acquisition (Schnappinger et al. 2003). Similarly, macrophages upregulate genes with functions related to immunity and inflammation to clear the invading pathogen. About 25% of the macrophage genome showed altered expression levels upon infection mainly driven by the macrophage-activating factor Interferon-$\gamma$ (Ehrt et al. 2001).

Her collaborative spirit became even more profound when Sabine was appointed Professor in 2010. She got involved in several global scientific projects, e.g. as chair of the Tuberculosis/Leprosy Panel of the USA–Japan Cooperative Medical Science Program, which fosters engagement between US and Asian scientists. Sabine was also involved on scientific advisory boards of several international research programs, including the Translational & Clinical Research Flagship Program Medical Research Council Singapore and the Research Unit at the University of Witwatersrand in Johannesburg. Being a member of the European Academy of Microbiology and section editor of their journal *microLife* fosters her belief that 'science is and should not be limited to a single country or continent as it is important to collaborate with other scientists globally and exchange knowledge'.

## Adapting to antibacterial attacks

Unfortunately, the collaboration between bacteria and other players is not always this mutual and beneficial. While we 'still don't know much about the lung microbiome and other microbes that *M. tuberculosis* likes to hang out with', we know that this pathogen learned to withstand attacks from its host. '*Mycobacterium tuberculosis* has evolved with humans and has evolved many strategies to resist the host environment', which is why it can stay dormant in macrophages for several years.

One defence strategy of macrophages to clear the intracellular pathogen is to lower the pH and oxidative state of the phagosome. However—as Sabine and her team found—*M. tuberculosis* produces a serine protease that is essential for the adaptation to such low pH (Vandal et al. 2008). This membrane protease triggers changes in the bacterial cell envelope to resist extracellular pH stress. Another important player in the pathogen's arsenal is the thioredoxin reductase TrxB2, which activates anti-oxidant pathways and redox-sensitive transcription factors as well as DNA- and protein-repair enzymes (Lin et al. 2016).

## Overcoming starvations of nutrients and research ideas

Better understanding of bacterial host adaptation mechanisms will eventually help identify efficient treatment strategies. 'Drug resistance is growing in importance. People need to recognise that without new treatments against drug-resistant bacteria and other microbes, we are really facing a global health problem.' This is also the reason why Sabine and her collaborators constantly aim to identify new drug targets, for which they focus on the bacteria's metabolic pathways.

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Upon macrophage infection, *M. tuberculosis* senses the presence of host lipids and thus switches its cellular metabolism to lipid assimilation and gluconeogenesis. Since phosphoenolpyruvate carboxykinase catalyses the first step of gluconeogenesis, this enzyme is essential for the bacterium's growth and survival within macrophages (Marrero et al. 2010). Another critical enzyme in the gluconeogenic pathway is fructose-bisphosphatase as it produces precursors for nucleotide and cell wall biosynthesis. Interestingly, Sabine and her team found that *M. tuberculosis* not only encodes one fructose-bisphosphatase but two, with each one being dispensable for virulence and survival (Ganapathy et al. 2015). Further characterising these novel enzymes is critical in the process of finding drugs to prevent this pathogen from growing within macrophages.

Just as *M. tuberculosis* is well adjusted to the macrophage environment, Sabine thinks that tackling this pathogen will require a flexible approach. As a researcher, 'you have to be able to adapt and be flexible, give up on ideas and come up with new ideas. So I think it's really important in research that you stay open-minded.' This is the same mindset Sabine displays as a team leader. 'I love meeting my lab members and what they bring into those meetings. It's not just about the data but the questions and ideas that are inspiring. I really enjoy working with people and mentoring students and postdocs.' This approach even brought her the Outstanding Teaching and Mentoring Award in 2020. It seems that her collaborative, supportive, and inspirational mindset also made an impression on her team.

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