

*Listeria monocytogenes* is a foodborne bacterium that can cause infection in humans, which lead to a serious illness called listeriosis and a high mortality rate (20–30%). To protect us, our immune system relies on specialized cells like macrophages, which are the first to recognize and fight invading bacteria. However, not all immune cells respond the same way — even when exposed to the same pathogen. Some react strongly, while others respond weakly or not at all. This cell-to-cell variability has long been considered a detrimental “noise”- allowing the bacteria to survive, spread and cause life-threatening infection. But our research suggests the opposite — that diversity in how individual immune cells respond may actually help the body defend itself. In particular, we have found that *Listeria* (and another common foodborne bacteria, *Salmonella*) suppress this variability as part of its infection strategy.

This variability in immune responses arises because genes inside our cells can randomly switch on and off, creating different levels of response in each cell. Communication between cells can further influence this variability. When we study immune cells that cannot communicate with each other, so that their responses become more uniform — we find that they become more vulnerable to *Listeria* infection. This suggests that variability may be protective.

Until now, we did not fully understand how this variation in cell responses is controlled. But our recent work reveals that what looks like random variation is actually tightly regulated at the single-cell level. This offers new insights into how we can measure this variability and how bacteria like *Listeria* manipulate our immune system.

In this project, we will investigate how *Listeria* manipulates immune cell variability, and how this affects infection outcomes. We will use cutting-edge methods to measure gene activity in tens of thousands of individual immune cells to identify which genes are involved, and how their variability is changed during infection. Using time-lapse microscopy, we will observe in real time how individual macrophages interact with *Listeria*, and how changes in gene regulation affect the course of infection.

To better understand these processes, we will use mathematical models to predict how *Listeria* manipulates host gene responses and how they play out during infection. We will use human immune cells taken from blood, as well as mouse infection models, to ensure our findings reflect real biological conditions - in the liver, a key site where *Listeria* spreads during infection.

This research will reveal how immune cells and pathogens interact with each other, uncovering mechanisms that control the success or failure of infection. In the long term, these discoveries could lead to new ways of treating or preventing bacterial infections - reducing the need for antibiotics. More broadly, this project will offer a new way to study how cells respond to infection or other challenges, helping us better understand the immune system and improve human health.