Universität Basel

# Research Project

# Tracking and manipulating Salmonella subsets in infected tissues over time

## Third-party funded project

**Project title** Tracking and manipulating Salmonella subsets in infected tissues over time
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**Organisation / Research unit**
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**Status** Active
This project intends to build a basis for **entirely novel strategies in infection control**, by broadening **successful host antimicrobial attacks**, and **closing permissive niches** in which pathogens can thrive.

Systemic *Salmonella enterica* infections are a **major cause of mortality** worldwide [1−5], and become increasingly untreatable [6,7]. Our **single-cell data** show in a mouse model that the host immune system actually **eradicates many *Salmonella* cells**, while other ***Salmonella* thrive** at the same time in the same tissue, causing lethal disease progression [8,9]. Emerging evidence suggests that similar heterogeneous host-pathogen encounters might be a key feature of many infectious diseases [10−20]. This heterogeneity offers **fascinating opportunities for research and application**. If we understand the mechanisms that determine the disparate local outcomes, we might be able to tip the balance in favor of the host, by **closing permissive niches in which pathogens can thrive**.

Current research mostly relies on **snapshots** that cannot capture the **crucial temporal dynamics**. We know that *Salmonella* cells differentially access host nutrients, experience oxidative or nitrosative stress, etc.; but what is the consequence of these encounters and **what impact do they have for overall disease outcome**? We detect many dead *Salmonella* cells in tissues; but which events **led to their killing**, and why did this **not happen** to the thriving *Salmonella* subset?

Our **goals** are, therefore, **to track *Salmonella* cells that have experienced a specific host encounter, to manipulate their fate, and to elucidate underlying mechanisms** in vivo. To achieve these goals, we will follow four specific aims, in which we test eight specific hypotheses:

1. To unravel encounter consequences over the **first few divisions** (6-36 h). We will exploit a fluorescent TIMER reporter variant with very slow color maturation as a novel tool.
2. To unravel encounter consequences over **several days**. We will link *Salmonella* subset-specific promoters with genetic switches and reporters useful for lineage tracing.
3. To determine the impact of specific encounters for **overall disease outcome**. We will deplete *Salmonella* in defined encounters using suicide lysis and/or DNA damage.
4. To determine the **underlying molecular mechanisms**. We will correlate local abundance of host factors with key encounter types and validate causal relationships using perturbations.

Combination of these innovative approaches with our recently developed 3D imaging technique for whole spleen will enable us to validate, improve, and extend our **spatio-temporal model for *Salmonella* infection dynamics**. This will be a key step for translating the increasingly detailed knowledge about *Salmonella* and host heterogeneity during infection, into **new strategies for controlling life-threatening systemic *Salmonella* infections**. We hope that our methods and concepts may inspire similar studies in **other major diseases** with a decisive role of heterogeneous host-pathogen encounters, such as tuberculosis[21].

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**Add publication**

**Add documents**

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