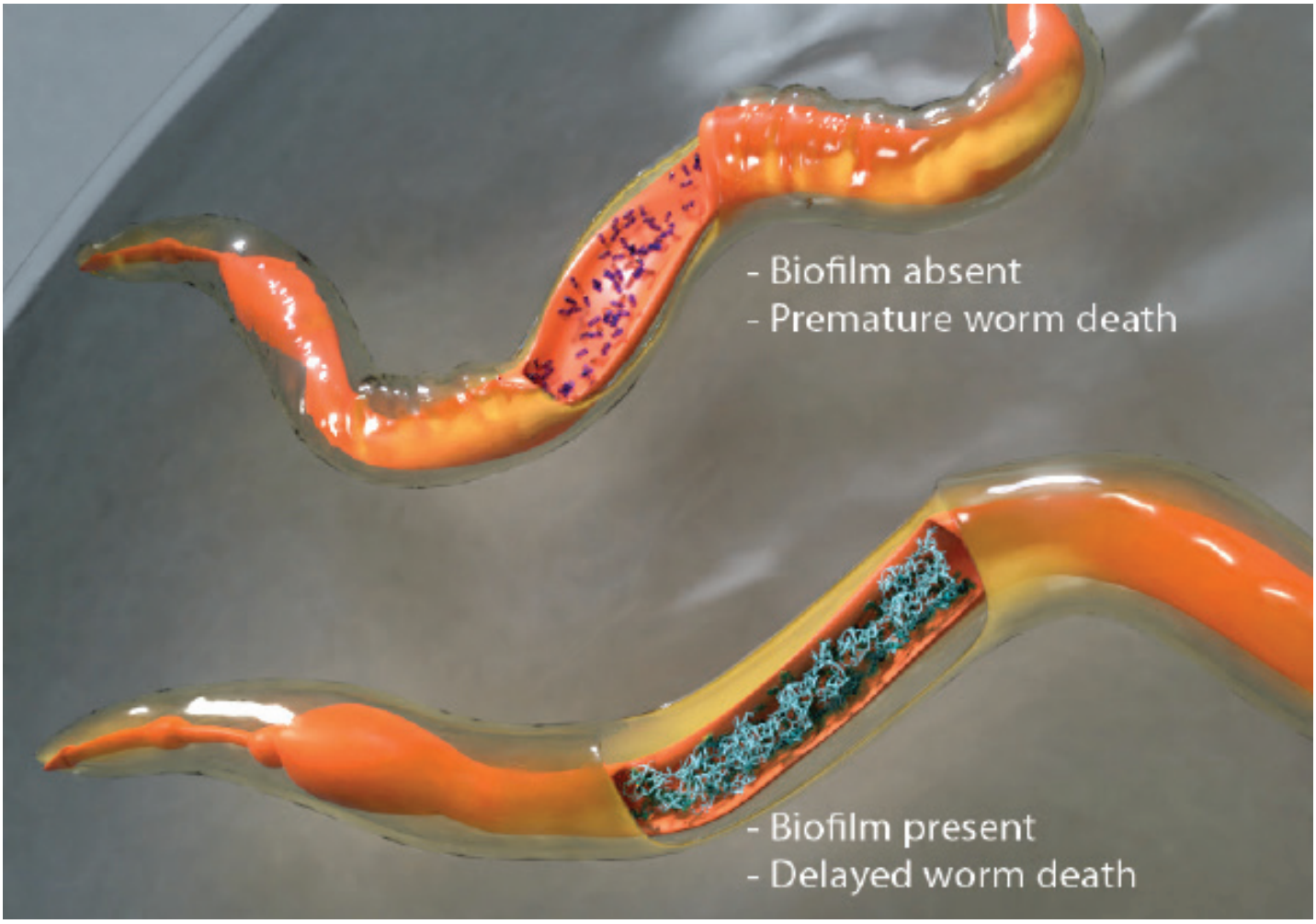


# Why *Salmonella* decide to lay low

## Studying dormant biofilms in live worm hosts

*Salmonella* can adopt either a virulent or a dormant lifestyle inside its host. Dormant states are characterized by the formation of biofilms inside the host and the molecular mechanisms that lead to the formation of biofilm inside live worm hosts were identified in this recent study led by MBI Senior Research Fellow Dr Stuti K Desai and Principal Investigator Professor Linda Kenney. The study was published in PNAS.

Illustration: Artistic illustration showing how the different *Salmonella* lifestyles inside the *C. elegans* worm affects host survival. In the absence of biofilm formation (top image), bacterial virulence pathways are activated leading to premature death of the host. However, dormant *Salmonella* forms biofilms (bottom image, blue), which offers an adaptive advantage and allows *Salmonella* to persist for a long time inside the host and delays worm death.

### Linda Kenney

Principal Investigator at the Mechanobiology Institute; Professor at the Department of Biochemistry and Molecular Biology, University of Texas Medical Branch, Galveston. The Kenney Lab is interested in studying signal transduction and regulation of gene expression during bacterial pathogenesis.

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### Reference

Desai SK et al. *Salmonella* biofilms program innate immunity for persistence in *Caenorhabditis elegans*. PNAS. 2019. 116(25). 12462-12467. doi: 10.1073/pnas.1822018116.

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# SsrB is indispensable for biofilm formation in *C. elegans* lumen

Written by Sruthi Jagannathan, Illustration by Diego Pitta de Araujo | June 2019

Most of us have endured a *Salmonella* infection at least once in our lifetime. These notorious bacterial pathogens affect over 17 million people worldwide every year in the form of mild food poisoning (most common), a more debilitating gastroenteritis, or a severe, even life-threatening case of typhoid fever.

What makes *Salmonella* such an expert pathogen is its ability to switch lifestyles inside its host, depending on the environmental conditions that it encounters. Under favorable conditions, *Salmonella* activates its repertoire of virulence genes, which allows it to invade host cells and actively spread infection. However, when host conditions are not so favorable, a different set of dormancy genes are activated that allow the bacteria to lay low and form clusters called biofilms inside their host. The biofilms either switch back into an infectious lifestyle or persist as dormant colonies, depending on whether favorable conditions return or not.

An earlier study led by Senior Research Fellow Dr. Stuti K. Desai from the Kenney Lab at the Mechanobiology Institute, National University of Singapore had unraveled the regulator that is important for controlling the lifestyle switch in *Salmonella* (Desai et al. eLife, 2016). This protein, called SsrB, belongs to a two-component regulatory system – the SsrA/SsrB system.

The way the SsrA/B two-component regulatory system works is relatively simple. SsrA acts as a sensor of the host environmental conditions. Based on the specific signals that it receives, SsrA activates the virulence pathway mediated by its partner, SsrB. Under dormancy conditions, the SsrA kinase is nearly absent and SsrB activates the dormancy genes.

Not only did Dr. Desai's study identify SsrB as the molecular controller that allows *Salmonella* to choose between virulent and dormant lifestyles, but she also highlighted the key role that SsrB played in mediating biofilm formation, as *Salmonella* strains lacking SsrB did not form biofilms (reviewed in Desai & Kenney, 2017).

However, as this previous study was carried out on lab-grown cell cultures, the question of whether the molecular mechanisms that controlled biofilm formation in cell cultures were identical to the mechanisms regulating biofilm formation in live *Salmonella*-infected hosts remained unanswered. Attempts at studying biofilm formation in live hosts have been made using other model organisms, including mice. But the difficulty of imaging *Salmonella* bacteria in mice tissue provides a substantial challenge in studying biofilms in this model system.

## *Salmonella* form biofilms in the lumen of live worms

In search of a simpler organism for studying biofilm formation, Dr. Desai collaborated with Dr. Anup Padmanabhan (Zaidel-Bar Lab, MBI), who was working on the nematode *Caenorhabditis elegans* (*C. elegans*), a microscopic roundworm. *C. elegans* offers several advantages over mice: they are transparent and therefore their internal structures can be imaged better. They are also hermaphrodites (both male and female reproductive organs exist in a single organism) and genetically less complex, meaning that the generation of mutant offspring is comparatively quicker and easier to study. More importantly, the mode of *Salmonella* infection in *C. elegans* is unique – the bacteria are found only in the lumen and do not invade cells, further simplifying the visualization of *Salmonella*.

In this study, the researchers infected worms with wild type *Salmonella* and mutant strains lacking SsrB, and employed a combination of immunofluorescence and confocal live imaging techniques to study the bacterial lifestyle inside the worms over several days post-infection. They observed biofilms in the intestinal lumens of *C. elegans* that were infected with wild type *Salmonella*; these biofilms shared similar characteristics with the biofilms that they had observed in their earlier in vitro studies. Interestingly, worms infected with mutant *Salmonella* were unable to form biofilms, which affirmed their earlier findings that SsrB was indispensable for the formation of *Salmonella* biofilms.

The researchers made another important revelation: there was a clear association between biofilm formation and the survival of the host. Biofilm formation disrupted virulence pathways that would otherwise kill the host and also promoted innate immunity signaling pathways in the host. Together, the findings suggest that by augmenting host defense mechanisms, biofilm formation offers an adaptive advantage and allows *Salmonella* to persist for a long time inside its host.

In humans, individuals harboring *Salmonella* biofilms remain asymptomatic carriers, but they are potential germ factories capable of spreading the disease to others. A classic instance in the early 20th century is the case of Typhoid Mary, an Irish cook and an asymptomatic *Salmonella* carrier, who unknowingly infected several members of the households where she worked. A number of these individuals who contracted the infection eventually died from typhoid fever. Therefore, understanding how and why this asymptomatic, dormant state exists inside the host is as important as studying the virulent, pathogenic state of the bacteria, in order to prevent major *Salmonella* outbreaks within communities.

In this regard, findings from the present study offers key insights into the characteristics of dormant persistence of *Salmonella* inside a live host. It also uncovers how the molecular mechanisms that drive biofilm formation under laboratory conditions are equally relevant in living systems. This study enhances the possibility to translate any knowledge obtained in the lab into tools for tackling bacterial persistence and pathogenesis in living hosts.

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