Structural analysis of the inter-membrane bacterial secretosome

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Project description:
Protein secretion is essential for life. Bacteria secrete proteins for a wide range of membrane and extracellular activities, including envelope biogenesis, pathogenicity and degradation of antibiotics. The major route for this process is via the ubiquitous Sec machinery of the bacterial plasma membrane. Your project would concern the mechanism of this process and subsequent poorly understood downstream transit through the bacterial envelope, and ultimately the biogenesis of the Gram-negative outer-membrane.

Gram-negative bacteria possess a cell wall composed of a periplasm with a peptidoglycan (PG) layer, surrounded by an outer-membrane. How does the bacterial cell ensure rapid and specific sorting of secreted protein for folding into the periplasm, or delivery to the outer-membrane, all done in the absence of energy? The mechanism of ATP driven transport across the inner-membrane by the Sec machinery is relatively well understood. Quality control systems are in place to ensure folding or, if required, degradation of resident periplasmic proteins. However, the route for outer-membrane proteins to the beta-barrel assembly machinery (BAM) is less clear.

We have identified an interaction between the bacterial holo-translocon (HTL) with a periplasmic chaperone and BAM, forming a structure that spans the entirety of the cell envelope. This giant assembly –the bacterial secretosome– could form a contiguous conduit for efficient passage of proteins from the cytosol to the outer-membrane. Its existence will have far reaching implications for our understanding of outer-membrane biogenesis [see recent pre-print from our lab: Alvira et al. 2019: https://doi.org/10.1101/589077].

Given that the cell wall is prone to attack, it is a target for many antibiotics, such as the □-lactams. Obviously then, the connection between the Sec and Bam machineries is rife for targeting; subversion of this interaction will disturb cell wall biogenesis essential for survival, and hence have the desired antibiotic activity.

The project will harness complementary technologies to explore the interplay of the translocons of the inner and outer membranes. Therefore, the project will offer training opportunities in a wide range of biochemical and biophysical techniques, including high-resolution electron cryo-microscopy (cryo-EM) and -tomography (cryo-ET). Moreover, as this is an unexpected and exciting new area of bacterial biology, you will have very good prospects for discovery. This could be through the exploration of fundamental features of the structure and function of the secretory machinery, as well as for the development of new strategies for drug development.