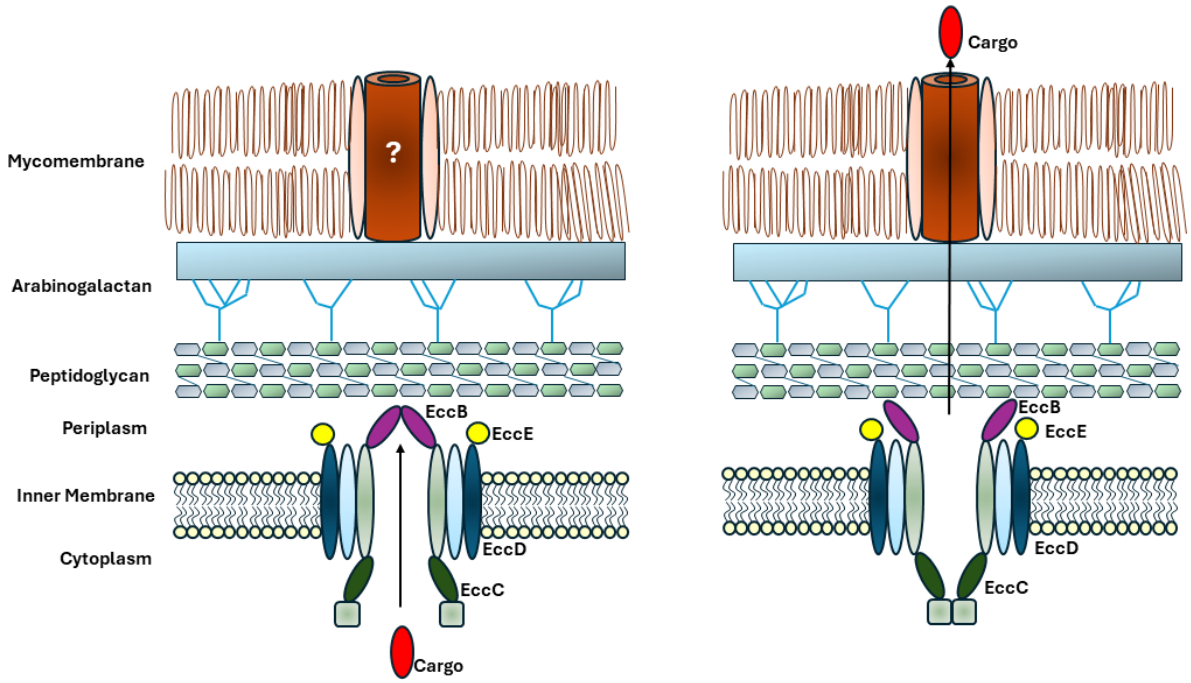
# Type VII Secretion System (T7SS)

(Carlos Medina Morillas)




**What function does it serve?**

The T7SS is a sophisticated nanomachine that exports proteins into the extracellular environment throughout the heavily lipidated cell wall of certain Gram-positive bacteria, such as mycobacteria or corynebacteria. Although it is not strictly dedicated to secreting toxic effectors in pathogenic bacteria, its importance relies on its critical role in the host survival strategy of *Mycobacterium tuberculosis*, the main causative agent of tuberculosis.

**What does it look like? How big is it?**

This system is like a big tunnel composed of proteins embedded in the plasma membrane that actively releases proteins to the tiny periplasm of mycobacteria. The cargo proteins are apparently subsequently directed to another, as yet unknown, channel that presumably traverses the mycomembrane to finally be delivered to the extracellular milieu. The T7SS size is around 28.5 nanometres in width and 20 nanometres in height.

**How does the cell make it?**

The T7SS substrates are synthesized in the cytosol, folded, and then transported across the cell envelope with the help of accessory proteins that bind to the substrates and target them to the secretion machinery, previously synthesized and assembled in the plasma membrane of the mycobacteria.

**How does it work?**

The precise mechanism of action of this system is not clear, since the translocation across the mycomembrane remains obscure. However, there are two proposed models that share some similarities. A cytoplasmic ATPase powers the protein secretion, and the inner membrane structural component EccC can adopt an extended or contracted conformation to open or close

the tunnel. In a one-step model the T7SS substrates could form a channel that connect the inner membrane machinery with the mycobacterial cell surface. A two-step transport is also hypothesized in which the cargo is transported into the periplasm to be somehow guided to a yet unknown pore of the mycomembrane that releases it to the environment.

**Where is it found? Which organisms?**
This system is found primarily in Gram-positive bacteria, specifically in the phyla Actinomycetota (e.g. *Mycobacterium*) and Bacillota, formerly Firmicutes (e.g. *Staphylococcus*, *Streptococcus*, *Listeria*), for which it is classified as T7SS and T7SSb, respectively. Less commonly, a "Type VII-like" secretion system has been observed in some Gram-negative bacteria. The strains harboring this system are pathogenic or non-pathogenic. In the latter case, the system is devoted to killing bacterial competitors.

**Some numbers**
The T7SS was **first discovered** in the pathogenic bacterium *Mycobacterium tuberculosis*, where it plays an important role in virulence and secretion of proteins across the unique mycobacterial cell envelope. In this bacterium, **five distinct paralogous secretion systems** have been identified. Each of these systems secretes different proteins during the infection process, playing crucial roles in the bacterium's ability to infect and cause disease. In other mycobacteria, not all these systems are present, revealing a specialization of each system in different environments.

**Its importance to the microbe?**
The T7SS found in mycobacteria plays a critical role in virulence and host immune evasion, its five variants being involved in distinct functions like phagosome rupture and prevention of its repair, delayed phagosome maturation and nutrient uptake. In contrast, the T7SSb of Bacillota functions in interbacterial competition through the secretion of toxic effectors which allows these bacteria to outcompete and kill closely related strains that lack the appropriate defense mechanisms.

**Its importance to us?**
Understanding this system provides new scenarios for targeting the human pathogen *Mycobacterium tuberculosis,* since the rise of multidrug-resistant strains is worrying. Traditional antibiotic treatments are becoming less effective against these newer strains and, additionally, they can collaterally damage the native microbiota. Therefore, the development of drugs against the “almost exclusive” protein secretion system of this type of pathogens is being explored as new target.