

Structural biology of type VII secretion machines

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Type VII secretion machines play key roles in the secretion of effector proteins in pathogenic bacteria such as *Mycobacterium tuberculosis*, the main causative agent of tuberculosis. This pathogen, still accounting for 1.5 million deaths worldwide annually, relies on five functionally distinct type VII secretion systems to survive in the host and efficiently evade its immune response [1].

The constituents of type VII secretion machines are known, but detailed information about their arrangement in the membrane has been scarce. Recently, we determined the cryo-EM structure of a stable core complex of one of these secretion nanomachines [2] revealing for the first time the intricate network of interactions of different components in the cytoplasmic membrane (Fig. 1). This structural information-

added to recent advances in the molecular biology of type VII secretion machines and its secreted effector proteins- provided first clues about the inner working of type VII secretion machineries. In this seminar I will present our structural model of the mycobacterial type VII secretion system, highlight the mechanistic implications of our study and discuss two derived transport models, which set up new scenarios for targeting the deadly human pathogen *M. tuberculosis*.

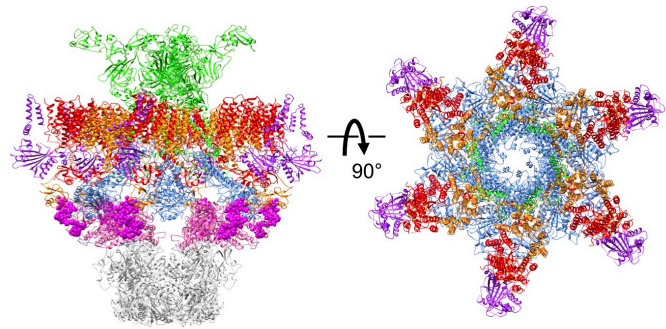


Fig. 1 Model of the T7SS core complex hexamer in the inner mycobacterial membrane derived from our cryo-EM structure of a dimeric building block [2].

[1] Rivera-Calzada A, Famelis N, Llorca, O and Geibel S (2021) Type VII secretion machines: structure, functions and transport models Nat Rev Microbiol. Sep;19(9):567-584. doi: 10.1038/s41579-021-00560-5.

[2] Famelis N, Rivera-Calzada A, Degliesposti G, Wingender M, Mietrach N, Skehel M, Fernandez-Leiro R, Bötcher B, Schlosser A, Llorca O, Geibel S (2019) Architecture of the mycobacterial Type VII secretion system Nature, 576:321-325