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Multiscale architectural dissection of the bacterial T6SS nanomachine to guide the design of virulence blockers targeting clinically relevant human pathogen

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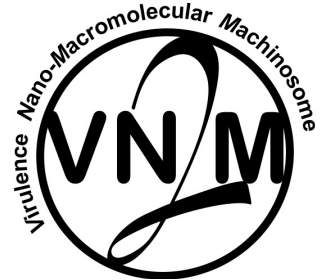
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Summary:

Human health is threatened by antibiotic resistant bacterial infection. The therapeutic options to handle this crisis are becoming sparse due to the multi-resistance of the “ESKAPE” bacteria that develops on antibiotics. New therapeutic options are urgently needed. A new strategy has recently emerged: instead of killing bacterial pathogens, one original concept consists of disarming them by targeting and blocking virulence mechanisms.

Virulence is based on the production of nano-macromolecular machines, not essential for bacterial life, some of which are involved in the traffic of toxic effectors across biological membranes. The type VI secretion system is used by pathogens, including ESKAPE bacteria to deploy their virulence when invading the human host. The T6SS is dedicated to the delivery of toxin proteins into eukaryotic and prokaryotic cells. There is accumulating evidence that T6SS is a key virulence factor during pathogenesis. Thus, inhibition of T6SS will adversely affect the virulence of pathogens by impairing their interbacterial competitiveness as well as their ability to modulate the local immune response and to colonize the human host. Considering the conservation of T6SSs across several bacterial human pathogens, discovery of an effective broad-spectrum T6SS virulence blocker should have major impact in worldwide human health.

The T6SS nanomachine is a multiprotein complex that is assembled across the bacterial cell envelope. The T6SS is composed of three architectural sub-complexes or “building blocks” that are well structurally characterized. Three proteins (TssB, TssC and Hcp) assemble a cytoplasmic contractile structure (tail-tube complex, TTC). This contractile device is anchored to the cell envelope by a membrane-spanning complex (MC) composed of four proteins (TssJ, TssL, TssM and TagL). We have recently gained insight into the intimate architecture, up to atomic details of the T6SS MC using an integrative approach combining cryo-electron microscopy (cryo-EM), X-ray crystallography and modelling. Finally, we have recently determined the atomic structure of the assembly platform, BP's building block, the wedge complex. We have demonstrated that the MC it is the first of the three complexes to be assembled and that its presence in the bacteria cell envelope dictates the assembly and positioning of the other two complexes (BP and TTC).

The final goal of our project is to target the assembly of the T6SS nanomachine with small molecule or peptide inhibitors, largely inspired by the high-resolution structures and molecular-scale data. The strategy we propose to engage is equivalent to “**a grain of sand in the T6SS gears**”. By sabotaging the nanomachine assembly, these future anti-T6SS drugs will be instrumental to block the virulence of Gram negative bacterial pathogens in the context of the antibiotics multi-resistance (AMR) crisis.

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