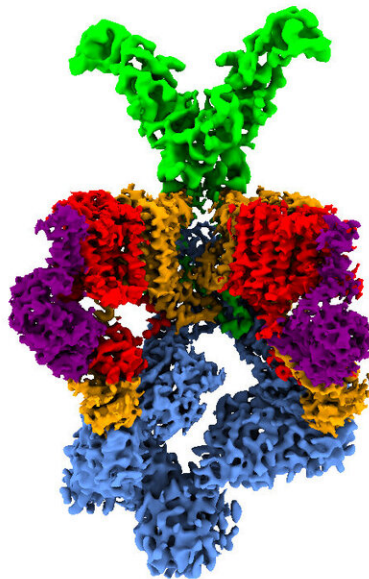


Scientists solve 3-D structure of 'nanomachine' that makes tuberculosis virulent

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3D structure of the T7SS secretion system of the bacterium 'Mycobacterium smegmatis', similar to that used by the tuberculosis bacterium during infection. The different proteins that make up this nanomachine are shown in different colors. In blue, elements of the system located inside the bacterium are responsible for trapping the virulence factors produced by the bacterium and providing the energy necessary for their secretion. In green, part of the system located outside the membrane of the bacterium, and that constitutes part of the pore by which virulence factors are secreted. Credit: CNIO

An international team headed by Óscar Llorca at the Spanish National Cancer Research Centre (CNIO), and the group led by Sebastian Geibel at the University of Würzburg (Germany), report an accurate 3-D model of the mechanism used by the bacterium *Mycobacterium tuberculosis* to block the immune response when infecting an organism.

This long-awaited finding is published in *Nature*. In a time when bacteria are increasingly developing resistance to antibiotics, ending the tuberculosis epidemic is one of the most urgent health issues of the Sustainable Development Goals established by the United Nations Organization (UN) for the year 2030.

Tuberculosis is an infectious disease with a [high mortality rate](#): It is one of the top 10 causes of death worldwide, and especially affects people with AIDS and other immunodeficiencies. According to data from WHO, 10 million people contracted tuberculosis in 2017 worldwide, and 1.6 million died. Since the current treatment has been in use for 40 years and new antibiotic-resistant strains of the disease are emerging, the need for new therapeutic strategies is urgent.

Bacteria against the immune system

When an organism is infected by *M. tuberculosis*, the [immune system](#) launches a complex response to destroy it. The bacterium has evolved several sophisticated mechanisms to undermine the immune system. The bacterium uses a [secretion](#) system—a [protein complex](#) located in its membrane—to inject certain [virulence factors](#) into the cells of the immune system. These factors are molecules that paralyze the defensive response of the immune cells so that bacteria have free rein to continue infecting the body.

The structure and operation mechanism of the *M. tuberculosis* secretion system, called T7SS (type VII secretion system), had not been studied in

detail. Until now, only very low-resolution structural information had been obtained, which showed a structure in the form of a hexamer (six-pointed star) whose center serves as a channel through which the bacterium ejects the virulence factors. The lack of information on T7SS and on how it works at the atomic level has prevented progress in achieving new therapeutic strategies against tuberculosis based on attacking the secretion system.

Now, researchers Óscar Llorca and Ángel Rivera-Calzada of CNIO, who contributed their expertise in cryo-electron microscopy (cryo-EM) and digital image processing, and Sebastian Geibel and Nikolaos Famelis from the University of Würzburg, experts in bacterial secretion systems, combined forces to unravel this puzzle. They have now described T7SS at the atomic level. The researchers worked with a very similar bacterium, *M. smegmatis*, which is used in research as a model to study *M. tuberculosis* and that shares the same secretion system with it. The work has shown that T7SS is a sophisticated nanomachine in which several proteins cooperate to inject the virulence factors produced by the bacterium into the cells of the immune system.

Toward a new generation of drugs

Recent developments have transformed cryo-EM into an extremely powerful technology that allows high-resolution imaging of molecular structures. This technique accelerates the obtaining of structural information that would otherwise require large volumes of the sample or its crystallization. With this technique, molecular biology and biomedicine are taking a huge qualitative leap that is expected to revolutionize the development of treatments of diseases.

In this paper, the researchers have pinpointed all the components of T7SS, and elucidated the function of some of them that remained unknown. They have also modeled its three-dimensional structure and

proposed an operating mechanism.

"We were able to see that the components that until now appeared blurred with other techniques are, in fact, elements that are in constant motion," explains Llorca. "Thus, we saw that the hexamer of T7SS is composed of a subcomplex of 4 proteins and that 6 identical copies of this subcomplex are needed to shape the six-pointed star around a central pore, through which the virulence factors that block the defensive response of the infected organism are ejected." Subsequently, the proposed mechanism was tested by the Würzburg University group using mutated versions of the system.

The system used by the German group to test the mechanism is also of great interest to the research community. "It will be very useful to test the effect of new molecules directed against this secretion mechanism, which the bacteria of the genus *Mycobacterium* need to successfully carry out the infection," explains Rivera-Calzada.

This multidisciplinary study opens a new field to explore for diseases caused by bacterial infections, since knowing the three-dimensional structures of bacterial [secretion systems](#) will allow exploring new compounds that block secretion. In the next steps of this research, the team of CNIO and the University of Würzburg will try to study in greater depth how the secretion process occurs in *Mycobacterium* to open the way to the design of molecules that can block it.

More information: Architecture of the mycobacterial type VII secretion system, *Nature* (2019). [DOI: 10.1038/s41586-019-1633-1](https://doi.org/10.1038/s41586-019-1633-1) , [nature.com/articles/s41586-019-1633-1](https://www.nature.com/articles/s41586-019-1633-1)

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