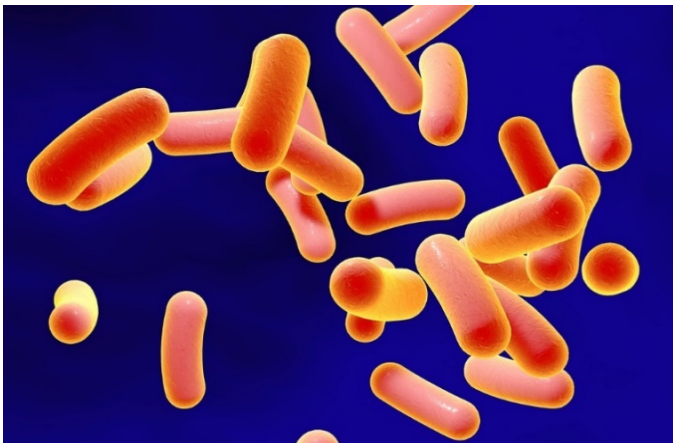
# noTBSec: New intervention strategy for tuberculosis by blocking multiple essential targets

## Challenge

*Mycobacterium tuberculosis* is the causative agent of tuberculosis (TB), a disease responsible for almost 1.3 million deaths per year. In recent years, different classes of drug resistant *M. tuberculosis* strains have emerged, making the discovery of novel anti-TB drugs a major global priority. A major disadvantage of most existing and new TB therapeutics is that they target a single molecule, which significantly increases the chance that resistant strains emerge. To prevent the rapid generation of antibiotic resistance it would be advantageous to block more than one essential target of the tubercle bacteria with a single drug.



## Research Approach

TB bacteria contain three different secretion systems that are essential for bacterial growth or virulence. A large compound library was screened for activity and toxicity tests. A few promising hits was extracted as potent inhibitors of the secretion systems (ESX-1, ESX-3 and ESX-5). A lead compound was identified that also showed synergistic activity with the antibiotic vancomycin.

## Project Outcome

The project has identified an inhibitor that targets multiple secretion systems. Further analyses are ongoing to elucidate its mechanism of action and patent is pending to be filed for the identified lead compound. The project has resulted in successful follow-up funding (TTW-NACTAR funding, The Netherlands) and generated interest for new collaboration with TB Alliance.

## Relevant publications

CESX-1 and phthiocerol dimycocerosates of *Mycobacterium tuberculosis* act in concert to cause phagosomal rupture and host cell apoptosis. Cell Microbiol. 19. e12726 (2017).

Mycobacterial ESX-1 secretion system mediates host cell lysis through bacterium contact-dependent gross membrane disruptions. Proc Natl Acad Sci U S A. 114:1371 (2017).

pks5-recombination-mediated surface remodelling in *Mycobacterium tuberculosis* emergence. Nat Microbiol. 1:15019 (2016).

## Research team

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