ID de Contribution: **7** Type: **Non spécifié**

Validation of Corynebacterium glutamicum as a surrogate for the discovery of new anti-mycobacterial compounds through the study of a well-established antibacterial target: DNA gyrase

Despite global efforts to combat tuberculosis (TB), the latest WHO report shows a total of 1.3 million people who died from TB, including 167 000 people with HIV. TB is the leading cause of death among HIV-infected patients, and the first leading infectious killer. Worldwide, multridrug-resistant TB (MDR- TB) is a major a public health problem and security threat. In order to eradicate TB, the main challenges include the understanding of the biology of *Mycobacterium tuberculosis (Mtb)*, the discovery and validation of new targets, the identification of new inhibitors with novel mechanisms of action (MOA) to treat multi- and extensively drug-resistant TB, as well as the development of new biochemical screens representative of the in vivo microenvironment.

In the lab, our goal is to develop a unified framework for the identification of new anti-tuberculosis drugs, relying on a non-pathogenic model organism, *Corynebacterium glutamicum.* The latter shares core characteristics with *Mtb*, such as its complex cell wall, that constitutes an important permeability barrier for antibiotics. We are setting up an in vivo cell-screening approach to test and indentify new actives drugs directly on the bacteria/our model organism. We will use the DNA gyrase, a validated target for anti-TB treatment, as a proof of principle for this assay (Petrella. S. 2019). The DNA gyrase is a type IIA topoisomerase capable of modulating DNA topology, essential for Mtb survival, thus making it a particularly interesting target for antibiotics. Our preliminary work shows that anti-gyrase inhibitors against *Mtb* are also active on the *C. glutamicum* gyrase. Indeed, these molecules confer a highly distinctive morphology on *C. glutamicum* that can be analysed using our cell-based assay. We are characterizing the mode of action of these inhibitors at the atomic level using cryo-electron microscopy in order to relate the detailed interactions between the DNA gyrase and the drugs to the morphologies identified. In parallel, we are also using *C. glutamicum* to identify the target(s) of compounds that have a confirmed activity against Mtb and that lead to a strong morphological readout in *C. glutamicum.*
I will present our work in progress and outline the detailed workflow of the project.

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