Call: 6th transnational call for the JPIAMR within the ERA-NET JPI-EC-AMR:
Innovations against antibiotic-resistant bacteria: New targets, compounds and tools

Title: Development of novel Mycobacterial Tolerance Inhibitors (MTIs) against MDR/XDR tuberculosis

Acronym: MTI4MDR-TB

Consortium composition

Type	Name	Institute	Country
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Abstract
In 2017, WHO published the Global Priority Pathogen lists with the aim to promote research and development of new treatments that are effective against microbes resistant to multiple antibiotics. Among them, multi- and extensively drug resistant *Mycobacterium tuberculosis* caused 48% of new tuberculosis (TB) cases in some countries in 2016. Current regimens for the treatment of TB include a combination of antibiotics developed for their strong efficacy against drug sensitive bacterium. The inadequacies of present TB therapies demand discovery of new agents with unique mechanisms of action to treat Mtb infection. Towards this end, we have discovered and developed a new family of ring-fused 2-pyridones (termed Mycobacterial Tolerance Inhibitors, MTIs) that potently sensitise Mtb to stresses encountered during infection and restores activity to the frontline antibiotic isoniazid (INH) in otherwise INH-resistant Mtb isolates. Our short-term objectives are to demonstrate preclinical proof-of-concept for MTIs to combat Mtb infection, optimise the current lead MTIs for translation to a therapeutic, and reveal new insights into pathways of drug tolerance and resistance. Our long-term objective is to develop a new orally available antibiotic that improves the current regimens for patients with drug-resistant TB. We will also generate a deeper understanding of the MTI's mode of action and their potential in synergistic interactions with other drugs. Importantly, we will also study how likely it will be for Mtb to develop resistance to combinations of MTIs and INH and other antibiotics.