MAIN RESEARCH LINES

1.Research of new antitubercular drugs and study of their mechanisms of action and resistance

Tuberculosis (TB) remains the leading cause of mortality from a bacterial pathogen, *Mycobacterium tuberculosis*. Indeed, TB caused by multi-drug resistant strains of *M. tuberculosis* (MDR and XDR) is a major threat to public health worldwide. There is therefore an urgent need for new anti-tuberculosis medications, which can counteract the phenomenon of drug-resistance. For this reason, since my PhD, I focused on the development of new compounds with antitubercular activity in early drug discovery phase, using innovative *in vitro* approaches for the identification and characterization of their mechanisms of action and resistance. In this path, I took part in the following international projects funded by the European Commission: "New Medicines for Tuberculosis" (NM4TB), "More Medicines for Tuberculosis" (MM4TB) and "European Regimen Accelerator For Tuberculosis" (ERA4TB). The latter project, ERA4TB, started in 2020 (January 1, 2020 - December 31, 2025) and has a duration of six years.

2. Study of the essentiality of genes coding for potential therapeutic targets of *Mycobacterium tuberculosis*

The validation of new therapeutic targets is fundamental in the process of characterizing the mechanism of action of new antitubercular drugs; in fact, thanks to gene regulation systems designed specifically for application in *M. tuberculosis*, it is possible to construct conditional mutants that can also be used in the drug discovery process. During the post-doc at the laboratory of Prof. R. Manganelli (University of Padua), I optimized the TetR-PipOFF gene regulation system and validated some important cellular targets (pyrG, mmpL3, pimA).
At the Molecular Microbiology Laboratory of Pavia, *canB* conditional mutants have been constructed in *M. tuberculosis* to characterize CanB carbonic anhydrase, a possible cellular target.

3. New weapons against *Mycobacterium abscessus* and other non-tuberculous mycobacteria

Non-tuberculous mycobacteria (NTM) are emerging as important pathogens in cystic fibrosis (CF) worldwide with an estimated incidence of approximately 3.3-22.6%. Among the NTM subspecies, *Mycobacterium abscessus* is becoming the most widespread and worrying pathogen in CF centres around the world. Drug therapy against *M. abscessus* lasts up to two years and its failure causes a rapid decline in lung function. Indeed, *M. abscessus* is intrinsically resistant to many drugs, thanks to its physiology and the acquisition of new drug resistance mechanisms (Degiacomi *et al*., 2019). Consequently, there is an urgent need for new and effective drugs against this pathogen with new mechanisms of action. Thanks to the projects funded by the Italian Cystic Fibrosis Foundation, FFC # 14/2020; FFC # 19/2018, we are testing new classes of compounds against the growth of *M. abscessus*: we have selected a molecule which is particularly effective against this emerging pathogen.