**Structure-function relationships and inhibition of enzymes involved in mycolic acid biosynthesis**

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*Mycobacterium tuberculosis*, the bacterium responsible for tuberculosis, and other mycobacteria have the particularity to synthesize a variety of specific lipids that contribute to the uniqueness and complexity of their cell envelope. These lipids play an extremely important role for the viability, virulence and pathogenicity, drug resistance and in the control of inflammation and immune response. These lipids include the preponderant mycolic acids, which form the mycomembrane of mycobacteria. **The biosynthetic pathway of mycolic acids is the target of known antituberculosis drugs and is a reservoir of potential therapeutic targets.**

Mycolic acids are high molecular weight α-alkylated β-hydroxylated fatty acids (containing up to 90 carbon atoms in *Mycobacterium*) which comprise various types of chemical modifications. Their biosynthesis involves two fatty acid synthase (FAS) systems and several enzymes required for the activation and the modification of lipidic or proteinic components.

This M2 project relies on a long-term collaboration with A. Quemard/F. Bardou/M. Ducoux/J. Marcoux in the research groups "Mycobacterial Envelopes and Therapeutic Targets" and "Proteomics and Mass Spectrometry of Biomolecules" at IPBS, which aims at characterizing enzymes involved in the mycolic acid biosynthetic pathway. The objectives will be to decipher, thanks to the study of the atomic structure of complexes with substrate analogues, the molecular mechanism of two deshydratases, HadAB and HadD. In addition we will study the mechanism of inhibition by the thiacetazone, an antibiotic of limited use due to its subsequent toxicity. This will give clues to develop thiacetazone derivatives of better therapeutic benefit.
Protocols for the production, purification, crystallization and measurement of the enzyme activity have already been partly developped. Some need futher improvments.

Discovery of a novel dehydratase of the fatty acid synthase type II critical for ketomycolic acid biosynthesis and virulence of Mycobacterium tuberculosis. Lefebvre C, Frigui W, Slama N, Lauzeral-Vizcaino F, Constant P, Lemassu A, Parish T, Eynard N, Daffé M, Brosch R, Quémard A. Sci Rep. 2020 Feb 7;10(1):2112.