The crystal structure of monoacylglycerol lipase form *M. tuberculosis* reveals the basis for specific inhibition

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Monoacylglycerol lipases (MGLs) are a class of enzymes that hydrolyze monoacylglycerol into a free fatty acid and glycerol. In bacteria, secreted MGLs can degrade bacteriotoxic monoacylglycerols and provide fatty acids originating from exogenous lipids. Fatty acids can be used for triacylglycerol synthesis, as energy source, as building blocks for energy storage, and as precursor for membrane phospholipids. In *Mycobacterium tuberculosis*, fatty acids also serve as precursor for polyketide lipids like mycolic acids, major components of the cellular membrane associated to resistance for drug treatment of the deadly pathogen.

In this study, we present the crystal structure of the MGL Rv0183 from *Mycobacterium tuberculosis* (mtbMGL) in open conformation. The structure reveals remarkable similarities with MGL from humans (hMGL) in both, the cap region and the α/β core. Nevertheless, mtbMGL could not be inhibited with JZL-184, a known inhibitor of hMGL. Computational docking experiments indicate possible interaction of JZL-184 with hMGL and provide an explanation why the activity of mtbMGL was not affected by the mammalian MGL inhibitor. Our findings suggest that specific inhibition of mtbMGL is possible without influencing hMGL and therefore provides a structural basis for rational design of a novel generation of inhibitors for one of the oldest recognized pathogens.