Monoacylglycerol lipases (MGLs) are a class of enzymes that hydrolyze monoacylglycerol into a free fatty acid and glycerol. Fatty acids can be used for triacylglycerol synthesis, as energy source, as building blocks for energy storage, and as precursor for membrane phospholipids. In mammals, inhibitors for MGLs are sought after to act as modulators of endocannabinoid signalling, cancer, neurodegenerative and inflammatory diseases. In *Mycobacterium tuberculosis*, the generated fatty acids also serve as precursor for polyketide lipids and mycolic acids, major components of the cellular membrane associated to resistance for drug treatment of the deadly pathogen.

3D structural knowledge of MGLs has become available only within the last years. We will present the crystal structure of the MGL from *M. tuberculosis*, *S. cerevisiae* and *Bacillus* sp. H257. These structures reveals remarkable similarities with MGL from humans in the α/β core as expected, yet unexpectedly also in the cap region despite the lack of significant sequence similarities. These cap modules provide the access path to the catalytic site and undergo conformational changes as observed in different crystals structures and using NMR dynamics and chemical shift perturbation studies.

Nevertheless, the available inhibitors appear to be rather specific for human MGL while not targeting MGL orthologs. This opens the possibility for specific inhibition of MGLs from pathogens without influencing human MGL. Therefore, these studies provide a structural basis for rational design of a novel generation of inhibitors for one of the oldest recognized pathogens.