IN VITRO PROFILING OF NEW ANTIMYCOBACTERIAL COMPOUNDS AND THEIR PEPTIDE CONJUGATES

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Tuberculosis is an infectious disease caused by the intracellular bacteria *Mycobacterium tuberculosis*. These pathogens live and reproduce in their host cells, mainly macrophages. Nowadays spreading of the drug-resistant strains of *Mycobacteria* is a serious health threat and there is an urgent need for development of novel compounds with no cross-resistance to current therapeutic options.

Salicylanilide derivatives have great potential as antimycobacterial compounds with pronounced inhibitory effect against not only *M. tuberculosis* but nontuberculous (also called atypical) mycobacteria (NTM), like highly chemoresistant *M. avium* and *M. kansasii*.

To enhance the cellular uptake of these antimycobacterial agents, they were conjugated to host cell-specific tuftsin peptide carriers. For the conjugation oxime and amide bonds were used. Oligo-tuftsin peptides $[TKPKG]_n$ (n=1, 2, 3) with and without enzyme cleavable linker sequences (GFLG, GFYA) were synthetized using Fmoc strategy. Amide bond was formed on resin and oxime bond was formed from the (aminooxy)acetylated derivatives of the peptides under acidic conditions.[1] Antitubercular effect (MIC value) was determined on *M. tuberculosis* $H_{37}Rv$. Cytotoxicity and cytostatic activity were determined on human monocytic MonoMac6 and hepatocellular HepG2 cell cultures. Intracellular efficacy was tested on *M. tuberculosis* $H_{37}Rv$ infected MonoMac6 cells.

In this study derivatives of hydroxybenzoic acids and their peptide conjugates were synthetized, characterized and *in vitro* evaluated. Minimum inhibitory concentrations (MIC) for both tuberculous and NTM were in the micromolar concentration range with moderate cytotoxicity and cytostatic activity on MonoMac6 and HepG2 cells. We have demonstrated that free compounds were ineffective on infected MonoMac6 cells, but peptide conjugates were active against the intracellular bacteria.

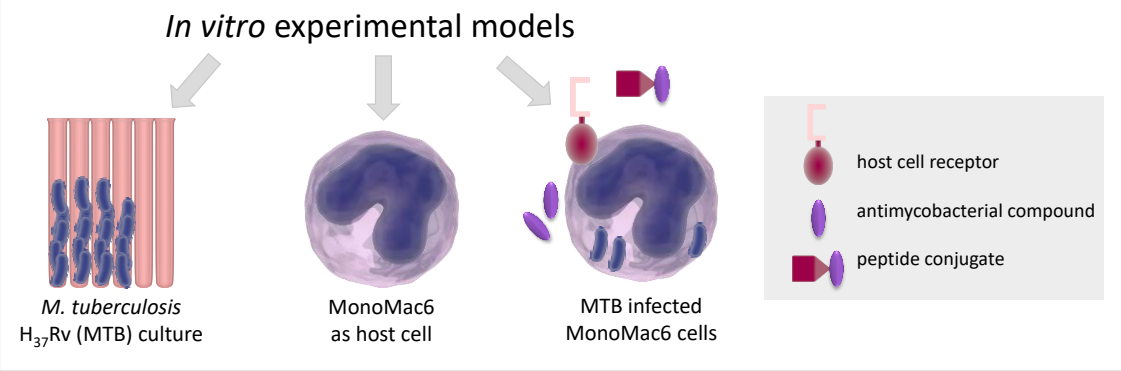

Fig.: *In vitro* evaluation of antimycobacterial compounds and their peptide conjugates

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