IMPROVED DRUG SUSCEPTIBILITY OF INTRACELLULAR *MYCOBACTERIUM TUBERCULOSIS*: THE IMPACT OF ANTIMICROBIAL PEPTIDE CONJUGATION OF ISONIAZID

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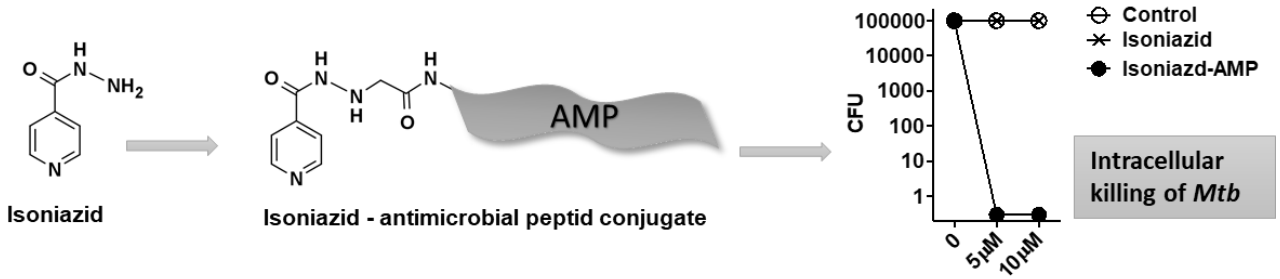
The main hallmark of tuberculosis (TB) is the ability of the causative agent to transform into a stage of dormancy in which the bacillus is shielded by an extremely robust cell wall and become phenotypically resistant to chemotherapy. *Mycobacterium tuberculosis* (*Mtb*) has the capability to modulate host phagocytes and evade phagocytic digestion mechanisms and in its intracellular form drug susceptibility of the bacteria is enormously low. Isoniazid is a first-line antitubercular drug used for the treatment and prophylaxis of TB. While Isoniazid is active against extracellular *Mtb* in the sub-micromolar range, the drug is not effective against the intracellular form even at 1000-times higher concentration[1]. Therefore, Isoniazid is a suitable model compound to study host-directed drug delivery and drug susceptibility of intracellular *Mtb.*

To improve cell penetration ability and intracellular killing efficacy of Isoniazid, antimicrobial peptide (AMP) based carriers were employed. AMPs can permeabilise the phospholipid membrane and/or cell wall and provoke a broad spectrum of antimicrobial activity against bacteria, viruses, and fungi. Despite the fact that bacteria are frequently exposed to AMPs, manifestation of AMP resistance is extremly low therefore an AMP-drug conjugates can act by multiple mode of antibacterial action without developing significant resistance. Nevertheless, internalization rate of the covalently attached drug to the host cells can be dramatically improved by AMP conjugation[2].



In this project, representative AMPs were employed as drug carriers and after careful *in vitro* evaulation a promising antibacterial drug conjugate with potent penetrating ability, antibacterial effect and suitable selectivity was tested *in vivo* in *Mtb* infected animal model.

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