A192 · Structural Optimization of Desotamide B for Combating Mycobacterium Tuberculosis

Presenter: Matthew Lin — Independent

Authors: Matthew Lin

Session: Day 1 · Thu Oct 1, 2026 · 2:15–4:15 PM

Antimicrobial resistance (AMR) is one of the most pressing threats to global health, threatening to undermine decades of progress in treating infectious disease. The World Health Organization has predicted that AMR could cause more annual deaths than cancer by 2050 (Vanheerentals, 2024). As conventional antibiotics lose effectiveness, the need for alternative antimicrobial strategies such as antimicrobial peptides becomes increasingly urgent.

Mycobacterium tuberculosis is classified by the WHO as a 'Critical Priority' pathogen due to its ability to develop resistance to traditional antibiotics, specifically rifampicin. It also presents a unique structural challenge: although gram-positive, its cell envelope is atypical, with a mycolic-acid-rich outer layer that functions like the outer membrane of gram-negative bacteria. To target this envelope, the non-ribosomal peptide Desotamide B, derived from the marine bacterium Streptomyces scopuliridis, was selected as a template. Based on the hypothesis that tryptophan- and arginine-rich sequences would improve the penetration of lipid-rich membranes, the original 6-residue peptide was extended to a 12-residue sequence to incorporate variations of tryptophan, arginine, and leucine to promote helical formation and balance hydrophobicity.

The redesigned peptide was optimized around amphipathicity as a central design parameter, achieving a value of 1.02, indicative of favorable membrane binding and insertion. The hydrophobic moment increased from 1.21 to 1.71, while the toxicity score shifted from −0.78 to −1.23 on ToxinPred, corresponding to a predicted 'Non-Toxin' classification. These results suggest that the engineered peptide retains strong membrane-disruptive potential while also minimizing toxicity.

These findings support the feasibility of using structure-guided mutation of natural AMP templates to design candidates against high-priority pathogens like M. tuberculosis. Future work should include experimental validation. For instance, the assessment of stability under physiological salt concentrations and the confirmation of lack of cell toxicity should be done to move this candidate toward practical therapeutic development.

Poster Submission Only