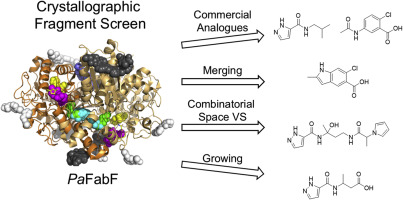
# Structure-based hit discovery for protein and RNA targets for antibiotics

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There is an urgent need for new antibiotics to prevent the looming crisis of antimicrobial resistance. Fundamental knowledge on new targets for antibiotics is critically needed, as are compounds that will penetrate bacteria and act on these targets [3]. To fuel the discovery pipeline, we are exploring proteins and RNA targets using a structure-based approach. For our protein-targeted drug discovery efforts, we have carried out fragment screenings against enzymes in the fatty acid synthesis pathway. Using biophysical methods such as bio-layer interferometry (BLI) and X-ray crystallography, we have discovered a number of covalently and non-covalently binding fragments which were then explored using different strategies (Figure 1) [1]. In the RNA area, we are focusing on riboswitches. These are *cis*-acting gene regulatory elements located in the 5' untranslated region of mRNAs.[2] Their widespread occurrence in bacteria combined with their regulatory role on gene expression through binding of small molecules makes them potential drug targets against a range of bacteria. We have discovered new ligands for the FMN and TPP riboswitches using a combination of structure-based based design, high-throughput screening and fragment screening. To support hit optimization, we have also dissected a previously reported drug-like FMN riboswitch ligand into smaller fragments to identify hot spots in the binding site. The insights gained from this analysis can now guide the optimization of the hit compounds.



###### **Figure 1**. Using crystallographic fragment screening, hits were discovered for FabF and subsequently elaborated using different methods. (Figure taken from [1]).

[1] Charis Georgiou, Ludvik Olai Espeland, Hemalatha Bukya, Vladyslav Yadrykhins’ky, Bengt Erik Haug, Prathama S. Mainkar, and Ruth Brenk. 2025. Towards new antibiotics: *P. aeruginosa* FabF ligands discovered by crystallographic fragment screening followed by hit expansion. *Eur. J. Med. Chem.* (April 2025), 117563. https://doi.org/10.1016/j.ejmech.2025.117563

[2] Vipul Panchal and Ruth Brenk. 2021. Riboswitches as Drug Targets for Antibiotics. *Antibiotics* 10, 1 (January 2021), 45. https://doi.org/10.3390/antibiotics10010045

[3] Ursula Theuretzbacher, Karen Bush, Stephan Harbarth, Mical Paul, John H. Rex, Evelina Tacconelli, and Guy E. Thwaites. 2020. Critical analysis of antibacterial agents in clinical development. *Nat. Rev. Microbiol.* 18, 5 (May 2020), 286–298. https://doi.org/10.1038/s41579-020-0340-0

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