**DEVELOPMENT OF NON-TRADITIONAL THERAPEUTICS AGAINST *PSEUDOMONAS AERUGINOSA***

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Peptide nucleic acids (PNAs) are synthetic analogs of DNA or RNA characterized by a neutral peptide-like backbone, providing exceptional stability and binding affinity for complementary nucleic acid sequences. This structure enhances resistance to enzymatic degradation, allowing PNAs to maintain their integrity and functionality in biological environments. These properties make PNAs effective tools for targeting specific RNA molecules, acting as antisense agents in therapeutic applications.1

In the opportunistic pathogen *Pseudomonas aeruginosa*, the small RNA (sRNA) ErsA acts as a post-transcriptional regulator implicated in virulence, biofilm formation, carbapenem resistance, and environmental stress responses.2,3,4 In a murine model of respiratory infection, ErsA has been demonstrated to contribute to pathogenesis by stimulating host inflammatory responses.4 Bacterial sRNAs like ErsA typically modulate gene expression by base-pairing with target mRNAs, thereby inhibiting or promoting translation.5

With the aim to reduce ErsA regulatory activity and potentially attenuate the virulence of P. aeruginosa, we designed eight PNAs targeting unstructured regions of ErsA sRNA. These PNAs were thought to act as antisense agents, inhibiting ErsA by preventing its interaction with target mRNAs. The neutral backbone of PNAs minimizes off-target effects, enhancing the precision of this antimicrobial strategy.

Our results demonstrate that targeting ErsA with PNAs effectively interferes with its regulatory function. Using a reporter system, we tracked the translation of the known ErsA target amrZ mRNA, demonstrating that two designed PNAs inhibited the ErsA/amrZ post-transcriptional regulation. Importantly, we show that anti-ErsA PNAs resensitized the multi-drug-resistant clinical strain RP73 to meropenem, showcasing their potential as precise antimicrobial agents.

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