Disarming Bacterial Pathogens with Peptide-Based Antivirulence Strategy

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Antibiotic resistance is accelerating and many severe infections, particularly those caused by *Staphylococcus* species, are increasingly driven by adhesion, immune evasion, and biofilm formation rather than rapid bacterial growth alone. Antivirulence therapy offers an alternative strategy: instead of killing bacteria, it aims to disable the molecular functions that enable infection, thereby preserving the microbiome and potentially reducing selective pressure for resistance.

I will present our peptide-inspired antivirulence targeting Sortase A (SrtA), the Gram-positive transpeptidase that covalently anchors LPXTG-motif surface proteins to the cell wall. These SrtA-anchored adhesins are central to early host attachment, clumping, and biofilm seeding in staphylococci, making SrtA an attractive upstream virulence target. Building on a substrate-derived inhibitor concept, we developed peptidomimetic SrtA inhibitors designed to engage SrtA with high specificity while maintaining drug-like properties and enabling systematic optimization through structure-activity relationships. A key focus of our work is in design, validation and translation.

I will discuss our framework for the complete assessment of SrtA inhibitors, combining orthogonal biochemical assays, and functional microbiology readouts such as adhesion/biofilm phenotyping and growth/viability profiling with pathogenic strains. Finally, I will highlight how this research can support advancement toward preclinical development and adjunct use alongside standard antibiotics.

References

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