Friday, November 14, 2025

Poster abstract submission

Approval Status Not Started

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Country Germany

Type of organization Academic / research institution

Poster title

Targeting Salmonella's virulence: Inhibition of the T3SS-2 major export apparatus protein SsaV by a synthetic small molecule

Poster abstract

The enteric pathogen Salmonella enterica serovar Typhimurium utilizes multiple effector proteins to invade and multiply within host epithelial cells, enabling systemic infection. Specialized secretion systems, such as the Type III Secretion System 2 (T3SS-2), encoded on the Salmonella Pathogenicity Island 2 (SPI-2), are essential for the translocation of these effector proteins into host cells, supporting intracellular survival, particularly within macrophages. This enables Salmonella to evade the host immune response by manipulating vesicle trafficking and maintaining the integrity of Salmonella-containing vacuoles (SCVs), thereby promoting bacterial persistence within the host.

The major export apparatus protein SsaV, located at the core of T3SS-2, is crucial for translocation of bacterial effector proteins into host cells. A functional SsaV is essential for Salmonella to establish infection and proliferate intracellularly. Therefore, targeting SsaV to block T3SS-2 function could represent an effective strategy to prevent systemic infections.

Through virtual docking, we identified a synthetic small-molecule binder V9. The in vitro binding of V9 to SsaV was validated by microscale thermophoresis (MST) using purified nonameric SsaV protein. We then used a split-luciferase host cell invasion assay that showed significantly reduced effector protein injection in V9-treated Salmonella. Consistently, Western blot analysis confirmed impaired effector protein secretion upon V9 treatment. Additionally, fluorescence microscopy and colony-forming unit assays in HeLa cells demonstrated reduced intracellular replication of Salmonella. To refine our understanding of V9 binding and improve the compounds efficacy, we performed alanine scanning mutagenesis and identified key residues whose substitution significantly impaired V9 binding. These complementary approaches will guide future structure-activity relationship (SAR) studies and hit optimization.

The inhibition mechanism of V9 offers a foundation for developing anti-virulence therapies targeting T3SS-2, with the potential to effectively treat Salmonella Typhimurium infections while minimizing the risk of promoting antibiotic resistance.

Research topic

Small molecule therapeutics