

Development of Novel Inhibitors Targeting VirF, the Key Virulence Regulator of *Shigella flexneri*

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Shigella flexneri, a gram-negative pathogen, is the main cause of bacterial dysentery in humans known as shigellosis. Infections by *Shigella* lead to over one million deaths worldwide each year, the majority of the victims being children under five years of age. The bacterium relies on various virulence factors that are essential to macrophage apoptosis and escape, intestinal epithelial cell invasion and cell-to-cell spread. These processes rely on a main transcriptional regulator, VirF, to activate transcription of the virulence genes. We hypothesize that antimicrobial agents can be developed to target VirF and inhibit virulence of *Shigella*. Targeting virulence factors required for infections is a relatively new strategy for developing antimicrobials. Since virulence factors such as VirF are not required for bacterial viability, inhibition of virulence pathways is expected to result in less selective pressure to develop resistance.

Previously, we conducted a high-throughput screen using a bacteria-based β -galactosidase reporter assay. From this screen, five lead compounds were identified to further pursue in hit-to-lead development. Using these chemical scaffolds, a structure-activity-relationship campaign will be conducted on a library of analogues to increase their potency. Commercially available compounds will be purchased and ones that are not available will be synthesized through collaborations with Dr. Showalter's lab and the Vahlteich Medicinal Chemistry Core (VMCC) at the University of Michigan. Activity of the compounds will be evaluated in an *in vitro* transcription assay utilizing VirF dependent transcription of RNA aptamers that bind malachite green upon the formation of a secondary structure. The mechanism of VirF inhibition of each promising compound will be determined and their cross-activity will be evaluated through virulence regulators of other pathogens. The identification of potent inhibitors will allow us to characterize the rate of resistance formation and potentially validate targeting bacterial virulence as a new approach for future antibiotics.

