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Inhibition of *Shigella flexneri* virulence regulator VirF

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VirF is an AraC family transcriptional activator that is required for the expression of virulence genes associated with invasion and cell-to-cell spread by including multiple components of the type three secretion system (T3SS) machinery and effectors. We tested a small-molecule compound, SE-1 (formerly designated OSSL_051168), which we had identified as an effective inhibitor of the AraC family proteins RhaS and RhaR, for its ability to inhibit VirF. Cell-based reporter gene assays with *Escherichia coli* and Shigella, as well as *in vitro* DNA binding assays with purified VirF, demonstrated that SE-1 inhibited DNA binding and transcription activation (likely by blocking DNA binding) by VirF. Analysis of mRNA levels using real-time quantitative reverse transcription-PCR (qRT-PCR) further demonstrated that SE-1 reduced the expression of the VirF-dependent virulence genes *icsA, virB, icsB, and ipaB* in Shigella. We also performed eukaryotic cell invasion assays and found that SE-1 reduced invasion by Shigella. The effect of SE-1 on invasion required pre-incubation of Shigella with SE-1, in agreement with the hypothesis that SE-1 inhibited the expression of VirF-activated genes required for the formation of the T3SS apparatus and invasion. We found that the same concentrations of SE-1 had no detectable effects on the growth or metabolism of the bacterial cells or the eukaryotic host cells, respectively, indicating that the inhibition of invasion was not due to general toxicity. Overall, SE-1 appears to inhibit transcription activation by VirF, exhibits selectivity toward AraC family proteins, and has the potential to be developed into a novel antibacterial agent.

Biography

Veerendra Koppolu is a Senior Scientist in Department of Biologics Development at AstraZeneca in Gaithersburg, Maryland, USA. He completed his Doctoral degree from University of Kansas, USA. He is an honorary faculty member at non-profit organization Novel Global Community Education Foundation (NGCEF) focused in guiding doctoral students. He has published over 46 papers including research article, review articles, abstracts, book chapters, and books. He is serving as Reviewer/Editor of 25 peer-reviewed international journals covering oncology and infectious disease areas. He is a member of American Association of Cancer Research (AACR), American Chemical Society (ACS) and American Association of Microbiology (ASM). His research interests include Pre-clinical and clinical development of monoclonal antibodies and novel small molecules as breakthrough therapies for cancer and infectious diseases.

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