Bacillus anthracis Antimicrobials Derived from Inhibitors of Mammalian Serine-Threonine Kinases

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Bacillus anthracis is a Gram-positive, spore-forming bacterium, and is the cause of anthrax. The nefarious use of *B. anthracis* as a bioterrorist agent with the potential release across densely populated areas is a major concern. Although *B. anthracis* is susceptible to a variety of antibiotics, the use of engineered, drug-resistant, strains must be considered. Hence, a comprehensive medical response to an intentional release of *B. anthracis* may need to include antimicrobials, which are not part of the traditional regimen. To this end, our group has been investigating the possibility of using inhibitors designed to target mammalian serine-threonine kinases (STK) as bactericidal compounds against *B. anthracis*. STKs, while abundant in mammalian cells, are found in limited numbers in bacteria, with *B. anthracis* encoding four such kinases; however, studies in other Gram-positive organisms suggest STKs regulate important aspects of metabolism and virulence. A panel of mammalian STK inhibitors was examined for antimicrobial effects on *B. anthracis*, and a single compound designed to target mammalian c-Jun N-terminal kinase (JNK) was found to prevent the growth of the organism. The JNK inhibitor (anthra (1,9-cd) pyrazol-6 (2H)-one; 1,9-pyrazoloanthrone) was found to be specific only for members of the Bacillus species. Further examination of the *B. anthracis* genome revealed a gene encoding for a protein (STK-1) with similarity to mammalian JNK, suggesting STK-1 as a possible target of the JNK inhibitor. However, a genetic knockout of the gene encoding STK-1 did not alter the growth of *B. anthracis* in rich media, but did reduce survival of the organism within macrophages. Finally, identification of mutants resistant to the JNK inhibitor required multiple passages of the organism through shallow increases in the concentration of inhibitor. Overall these findings suggest, the JNK inhibitor may provide a platform for development of new compounds targeting critical kinases in *B. anthracis*, and may serve a useful research tool for determining the role of kinases in the growth and survival of this important pathogen.