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Selective vitamin K_2 biosynthesis inhibitors to treat non-replicating *Mycobacterium tuberculosis*

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Abstract

The emergence of multidrug-resistant strains of *M. tuberculosis* (Mtb) seriously threatens TB control and prevention efforts. In general TB chemotherapy, a combination of four TB drugs is given for at least six to nine months for drug-susceptible Mtb infections. Thus, it is considerably important to discover promising approaches to shorten a TB drug regimen. Mechanisms that enter non-replicating state of Mtb are accounted for a significant factor that requires long-term chemotherapy. Therefore, new drugs that target non-replicating Mtb are likely to revolutionize TB chemotherapy. Majority of Gram-positive bacteria including *Mycobacterium spp.* utilize only menaquinone (vitamin K_2) in their electron transport systems, and menaquinone biosynthesis is essential for survival of Gram-positive bacteria. On the other hand, Gram-negative organisms utilize ubiquinone (CoQ) under aerobic conditions, and menaquinone under anaerobic conditions. Thus, inhibitors of menaquinone biosynthesis systems have great potential for the development of novel and selective drugs against MDR Gram-positive pathogens. We have discovered optically active MenA(the 6th enzyme in menaquinone biosynthesis) inhibitors that showed significant growth inhibitory activity against non-replicating Mtb (MIC_{LORA}, 0.85 □g/mL) with the MIC_{LORA}/MIC_{MABA} value of 0.37. The discovery of molecules that kill non-replicating Mtb at lower MIC (MIC_{LORA}) than the MIC obtained under aerobic conditions (MIC_{MABA}) is expected to be of significance in terms of discovering new lead molecules that can be developed into new drugs to kill Mtb in any states. I will present the assay protocol for identification of selective MenA inhibitors, and novel antimycobacterial MenA inhibitors that killed non-replicating Mtb at low concentrations.

Biography

Dr. Kurosu received his PhD from Osaka University (Japan), School of Pharmaceutical Sciences and broadened postdoctoral training and experience at Harvard University, Department of Chemistry and Chemical Biology. He is an Associate Professor at University of Tennessee Health Science Center. He has published more than 85 papers in reputed journals and has been serving as NIH study section reviewers. Dr. Kurosu has a long-term interest in development of new antibacterial agents targeting novel drug targets.