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Discovery of WecA inhibitors for development of new TB drugs for dormant Mycobacterium tuberculosis infections

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The emergence of multidrug-resistant (MDR) strains of *Mycobacterium tuberculosis (Mtb)* seriously threatens TB control and prevention efforts. In general TB chemotherapy, treatment length can be up to two years for infections of MDR strains and can be longer for extensively drug-resistant (XDR) strains. Thus, it is an important program to discover promising approaches to the shortening of current TB drug regimen. Mechanisms that enter non-replicating (or dormant) state of *Mtb* are accounted for a significant factor that requires long-term chemotherapy and new drugs that target non-replicating *Mtb* are likely to revolutionize TB chemotherapy. WecA, a phosphotransferase that catalyzes the transformation of prenyl-diphosphoryl-GlcNAc from UDP-GlcNAc and decaprenylphosphate, is essential in growth of *Mtb* under aerobic conditions and to survive for *Mtb* in macrophages under oxygen-depleted conditions. Our group developed a convenient assay method against WecA using the modified enzymatic substrates and an assay method to determine bactericidal effect of molecules against intracellular Mtb. As the results of screening of capuramycin-based analogs via our methods, we identified strong WecA inhibitors (low nanomol range concentrations) that kill replicating and non-replicating Mtb. The details of assay development and in vitro assay data for the identified anti-mycobacterial WecA inhibitors will be presented.

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