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# 結核菌の新薬ターゲットとしての PPTase。

尹　忠鉄

ホスホパンテテイニルトランスフェラーゼ(phosphopantetheinyl transferases :PPTase)は CoA からホスホパンテテイン基を脂肪酸合成酵素やポリケチド合成酵素 (PKS)、非リボソームペプチド合成酵素 (NRPS)などのキャリア蛋白質に転移して活性化させる酵素である。PKS や NRPS 生産物が多数の病原菌の病原性に関与していると言う報告から近年、PPTase をターゲットにした阻害剤スクリーニングが関心を集めているが現在までに有効な阻害剤は見つかっていない。本論文では結核菌の新薬ターゲットとして PPTase に注目し阻害剤を検索するため新しい high throughput スクリーニング系を提案したので紹介する。

## 紹介論文

4′-Phosphopantetheinyl Transferase PptT, a New Drug Target Required for *Mycobacterium tuberculosis* Growth and Persistence *In Vivo*.

Ce´cile Leblanc, Thomas Prudhomme, Guillaume Tabouret, Aure´ lie Ray, Sophie Burbaud, Ste´phanie Cabantous, Lionel Mourey, Christophe Guilhot, Christian Chalut

(CNRS, IPBS (Institut de Pharmacologie et de Biologie Structurale), Toulouse, France,)

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**Abstract**

The cell envelope of *Mycobacterium tuberculosis*, the causative agent of tuberculosis in humans, contains lipids with unusual structures. These lipids play a key role in both virulence and resistance to the various hostile environments encountered by the bacteria during infection. They are synthesized by complex enzymatic systems, including type-I polyketide synthases and type-I and -II fatty acid synthases, which require a post-translational modification to become active. This modification consists of the covalent attachment of the 4′-phosphopantetheine moiety of Coenzyme A catalyzed by phosphopantetheinyl transferases (PPTases). PptT, one of the two PPTases produced by mycobacteria, is involved in post-translational modification of various type-I polyketide synthases required for the formation of both mycolic acids and lipid virulence factors in mycobacteria. Here we identify PptT as a new target for anti-tuberculosis drugs; we address all the critical issues of target validation to demonstrate that PptT can be used to search for new drugs. We confirm that PptT is essential for the growth of *M. bovis* BCG *in vitro* and show that it is required for persistence of *M. bovi*s BCG in both infected macrophages and immunodeficient mice. We generated a conditional expression mutant of *M. tuberculosis*, in which the expression of the pptT gene is tightly regulated by tetracycline derivatives. We used this construct to demonstrate that PptT is required for the replication and survival of the tubercle bacillus during the acute and chronic phases of infection in mice. Finally, we developed a robust and miniaturized assay based on scintillation proximity assay technology to search for inhibitors of PPTases, and especially of PptT, by high-throughput screening. Our various findings indicate that PptT meets the key criteria for being a therapeutic target for the treatment of mycobacterial infections.