

## How to Kill Dormant *Mycobacterium Tuberculosis*

Sir,

Asymptomatic latent tuberculosis (LTB) infection is caused by dormant *Mycobacterium tuberculosis* (MTB) cells that are tolerant to antibacterial compounds due to their low level of metabolic activity. Consequently, despite the fact that the authors of some studies claim that a particular drug is active against dormant MTB cells, the relevance of dormancy models used in such studies makes these claims questionable. For example, in the very useful review article published in IJMYCO<sup>[1]</sup> the authors have discussed the efficacy of antitubercular drugs and their combinations against nonreplicating MTB obtained in different experimental models. However, anaerobic “Wayne’s MTB” and nonreplicating cells in other *in vitro* dormancy models exhibit quite a significant level of metabolic activity according to transcriptomic and metabolomics studies, which is evidently responsible for their sensitivity to drugs. Notably, in accordance with the Cornell *in vivo* mice model of LTB and some clinical studies, dormant cells in latently infected individuals are characterized by non-culturability (a phenomenon of transient inability to divide and grow on nonselective solid media) and require a resuscitation procedure to be uncovered in the samples.<sup>[2]</sup> Evidently, this population of nonculturable (NC) cells is responsible for persistence in organs and inefficiency of conventional anti-TB drugs.<sup>[2]</sup> In this regard, in the experimental *in vitro* model, which generates dormant NC MTB cells with negligible metabolic activity, known antitubercular drugs in conventional concentrations were found to be not active.<sup>[3]</sup> This finding is not surprising because many antimicrobials target biosynthetic pathways such as protein, nucleic acids or cell wall polymer synthesis that eventually leads to cell death, while dormant NC cells with negligible metabolic activity would escape the activity of such “biochemical drugs” regardless these cells still contain an appropriate target.

On this basis, we may suggest that killing effect for dormant NC cells could be provided by antimicrobials producing direct harmful effect on the cell which may modify cell constituents by alkylation, hydrolysis, reduction/oxidation, etc., (“chemical drugs”). Thus, 1-hydroxy-2-thiopyridines promote transportation of Cu<sup>2+</sup> in the mycobacterial cell by formation of a stable charged complex and accumulation of copper ions in poisoning concentrations resulting in killing effect for dormant NC MTB.<sup>[4]</sup> However, such compounds would likely be toxic for the host, so using prodrugs that will be

processed by the particular enzymes remaining in dormant MTB with the formation of active molecules with general toxicity or stimulating the activity of hydrolyzing enzymes seems to be more perspective. An example of the suggested approach is nitroimidazopyran PA-824 and its follow-up version delamanid, which are metabolically converted by mycobacterial F420-dependent deazaflavin-dependent nitroreductase with release of intracellular nitric oxide that results in nonspecific killing and eliminating NC MTB.<sup>[1,5]</sup> Clofazimine which generates intracellular reactive oxygen species due to redox cycling through nicotinamide adenine dinucleotide-oxidoreductase is also known to be capable to eliminate persisting mycobacteria.<sup>[1]</sup> It is important that the mutation rate in bacteria for both PA-824 and clofazimine is very low what is expectedly due to their nonspecific mode of action. Despite these compounds may be not superior in killing of replicating MTB, to our opinion, “chemical drugs” are perspective for combination therapy to eliminate the subpopulation of dormant NC MTB.

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### Conflicts of interest

There are no conflicts of interest.

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