Challenges in anti-TB drug discovery and the CDRI initiative

Sudhir Sinha

Drug Target Discovery and Development Division,
Central Drug Research Institute, Lucknow- 226001 (India)
Email: sudhir_sinha@cdri.res.in

ABSTRACT

WHO estimates that close to 2 million deaths occur due to tuberculosis every year and a third of world's population is exposed to or infected with *Mycobacterium tuberculosis*. Over 50% of deaths among HIV-infected persons are due to co-infection with *M. tuberculosis*. MDR-TB is increasingly common in different parts of the world. Moreover, a new and deadlier form of TB- XDR (extensively drug-resistant)- has emerged which is resistant to all first line and many of the second line anti-TB drugs.

During the past decade, emphasis has been placed on target-based drug discovery. The success of the target-based approach is dependent on the quality of target and the level of validation. Confidence that inhibition of the target will result in death of the microbe and resolution of infection is the essence of target validation. Our experience and those of others underscore the inadequacy of screening of compound libraries against isolated targets in the quest for novel anti-mycobacterial leads. The whole-cell assays are favored for finding a lead compound that has a modicum of antibacterial activity.

CDRI is running a priority programme on design and development of new therapeutics against TB. Over the years approximately 34,000 samples, comprising 16,000 synthetic molecules and 18,000 natural extracts (originating from plants and marine flora/fauna) have been subjected to anti-TB screening using high-throughput and conventional methods. The 'hits' were subjected to cytotoxicity evaluation against vero cells and mouse macrophages. The non-toxic hits were further evaluated in the mouse bone marrow macrophage model of TB. At least 9 molecules showed a better *ex vivo* activity than isoniazid or rifampicin. These were subjected to *in vivo* evaluation in the mouse model of TB. Two molecules have so far shown a significant anti-TB activity in terms of survival time and bacterial load in lungs of the infected mice. One of the active compound-class was designed to inhibit the fatty acid synthase-II (FAS-II) enzymes of the pathogen. The Institute is also working on target-based drug design. To this end, we have reported the crystal structure of adenylation domain of the NAD dependent DNA ligase of *M. tuberculosis*. The screen design group, on the other hand, is working on the development of new screens, including those aimed at elucidation of mechanism of action of lead molecules as well as standard drugs.