Editorial:

Mycobacterium tuberculosis: a perpetual health care challenge

Over thousands of years of history, *Mycobacterium tuberculosis* has proved to be a formidable human pathogen resulting in immense morbidity and millions of deaths. The number of new cases were 10.4 million along with more than a million deaths [in human immunodeficiency virus (HIV)-negative persons] in the year 2016.[1] With the advent of multidrug-resistant tuberculosis (MDR-TB), tuberculosis (TB) has re-emerged as an enormous challenge to public health systems world-wide, more so in developing countries like India.

First-line drugs commonly used for the treatment of TB are isoniazid (H), rifampicin (R), ethambutol (E), pyrazinamide (Z) and streptomycin (S) are administered in combination. Moreover, TB and HIV co-infection and the appearance of extensively drug-resistant TB (XDR-TB) have necessitated intense on-going research for discovery of novel drug targets and new drugs. Efforts are also underway for repurposing of drugs and innovative approaches, such as, genome derived target-based approach, multi-target pathway screens, redesign/engineering of existing scaffolds.[2] Further, newer drug delivery systems and innovative clinical trial designs, such as, multi-arm, multi-stage determinations of efficacy of newer anti-TB drug combinations ar also being tried out.[3,4]

Not many new drugs are visible on the horizon and the efforts at anti-TB drug discovery have been tedious and time consuming. Also, testing of new compounds against TB is considered to be an expensive, risk-prone low-yield and slow process since the drugs have to be monitored over a long period of time to establish their efficacy and identify potential side effects. Another problem pertinent to developing countries is emergence of drug-resistance because of irregular medication, overuse, misuse and abuse of antibiotics. If old drugs do not work and new drugs are not available, the doctors will end up facing shrinking treatment options.

Some of the work done in India at the Indian Institute of Science (IISc), Bengaluru, in this regard deserves mention. The group has identified a nucleoid associated protein HU as a potential drug target for treating TB.[5] HU protein plays an important role in maintenance of chromosomal architecture and in global regulation of deoxy ribonucleic acid (DNA) transactions in bacteria. HU is essential for the growth of *Mycobacterium tuberculosis* . The authors[5] have determined the crystal structure of a domain of the protein HU. Based on bioinformatics approach and molecular biology studies, group has identified a core region within the HU-DNA interaction interface that could be targeted using small molecules such as stilbene derivatives. These small molecules inhibit HU-DNA binding, disrupt nucleoid architecture and reduce the growth of *Mycobacterium tuberculosis*. This work[5] provides a proof of principle that nucleoid associated proteins in bacteria can be targeted using small molecules. However, such innovative ideas generated in the bench-work requires an enormous amount of additional research, eventually followed by clinical trials before such molecules can become available for human use.

Online access
http://svimstpt.ap.nic.in/jcsr/oct-dec17_files/edi.17.09.007.pdf
DOI: http://dx.doi.org/10.15380/2277-5706.JCSR.17.09.007

Despite years of efforts, not much is known concerning the biology of *Mycobacterium tuberculosis* during human infection and how it remains dormant in the host for extended periods of time. Basic research along these lines might not only enhance our understanding of the pathogen but also point to new treatment options. Method of retaining the dormant state so that symptoms are not manifested can be another line of treatment.

Financially disadvantaged section of people have access only to suboptimal nutrition and hence has less than ideal immune system.[6] They are more susceptible to TB infection and are solely dependent upon the public health system for treatment. It is laudable that the Indian government is strengthening public health programs for TB. The expectation may be that that TB will become insignificant in India within the next few decades based on such measures. However, there is every possibility that new strains of *Mycobacterium tuberculosis* will emerge which may be highly resistant to the existing drugs. The new drug-resistant strains can originate anywhere in the world, but can easily travel to India within a short period of time due to international travel. Then the frightening question arises, what should be done if the new *Mycobacterium tuberculosis* strains are resistant to all the existing drugs with no new drugs in the pipe line?

Hence a holistic multi-pronged multi institutional approach needs to be pursued which involves improvement of the general well being of the population, preventive measures, proper use of antibiotics, monitored treatment of TB patients, and needless to say, rigorous basic research with a view to develop novel anti-microbial compounds.[7] Only such an approach will help in reaching the goal of defeating *Mycobacterium tuberculosis.*

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Received: September 28, 2017, Accepted: September 30, 2017.

Ramakumar S. *Mycobacterium tuberculosis:* **a perpetual health care challenge. J Clin Sci Res 2017;6:201-2; DOI: http://dx.doi.org/10.15380/2277-5706.JCSR.17.09.007.**

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