Tuberculosis research in India

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Tuberculosis is a highly prevalent infectious disease and globally, India is one of the 22 high-burden countries. There are diagnostics and drugs available and vaccine initiatives to control the disease. However, the need of the hour is improved Point of Care diagnostic; less toxic but cheaper drug of short duration and a new vaccine is of utmost importance. Also, other areas need to be strengthened. For these, research efforts are ongoing and Indian researchers have been involved in several diversified fields of this endeavour. This commentary deals with some of the notable research works in the recent past.
Institute, Gurgaon has worked on new diagnostic modalities with novel TB biomarker and PoC test exploiting antigen and nucleic acid.

JALMA, Agra has signed a contract in 2007 with the Nutrapharma, USA for diagnostics of NTM through designer diagnostics NTM kits, the most predominant one as found is the M. avium complex in soil and water. It has patented the new efflux pumps active in the multidrug resistance (MDR), INH resistance and ofloxacin in Mtb. PCR-RFLP has been developed with 23S rRNA gene region restricted with HhaI enzyme for speciation of mycobacteria. Another researcher has extensively worked on epidemiology and pathogenesis of TB; also molecular insights into spread of MDR TB in India.30,31

The group led by Hasnain (IIT, Delhi) has focused on the PE/PEP proteins involved as diagnostic marker, cell signaling, host-pathogen interaction, molecular mimicry, etc.12. The predominance of the less virulent, ancestral strains of Mtb circulating in India; India’s first whole genome sequencing of Mtb; the immuno-modulatory role and biomedical importance of soil Mw, renamed as MIP/Mycobacterium indicus pranii have also been studied by him.

Several indigenous or imported serological tests have been performed for rapid diagnosis in most of the private healthcare sectors in India. However, no perfect test has come up with excellent performance and recently, WHO, Geneva has issued a negative policy9 on the use of any serological test. However, it does not imply banning of research on development of any novel serological test.

Cepheid, USA through FIND, has launched GeneXpert MTB/RIF, to diagnose TB and MDR TB which takes two hours for results and seems better than the microscopic evaluation. This is being evaluated in India. STOP TB Partnership has mediated a clinical trial of Signature Mapping Medical Sciences, USA developed automated TB detection system (TBDx) for Auramine-O stained slides through Apollo Hospitals.

Bigtec Laboratories, Bangalore and the Tulip Group, Goa have jointly developed a hand held battery-powered and cheap polymerase chain reaction (PCR) test to be used in peripheral settings, through CSIR’s NMITLI programme and GCC. A PCR test has been developed by Xcyton in partnership with a public research group funded by NMITLI programme. A multiplex PoC diagnostic platform based on microfluidics has been launched by Achira Labs, Bangalore, which has explored an innovative technology of hand-woven silk ‘chips’ supported by GCC. TB-specific glycolipids have been explored by Jiwaji University in partnership with Bisen Biotech, Gwalior to develop a TB test9.

**TB drug development**

Efforts in India have included the sudoterb by Lupin Ltd, Mumbai for which the Phase I Trial has been cleared and the next phase to assess the bactericidal effect has begun. The safety trial of benzothiozainone by AstraZeneca, Bangalore has also started. The Central Drug Research Institute, Lucknow has developed inhalable microparticles for PTB. One very new and innovative example can be cited as the Open Source Drug Discovery (OSDD), by CSIR as a Consortium acting as a global translational platform for drug discovery. Currently, through the TB Drug Alliance effort, India has entered into a global clinical trial for three drugs namely Sirturo/bedaquiline, PA 824 and Delamanid for treating both drug-sensitive and drug-resistant TB. AIIMS and NIRT have also been doing trial for Bedaquiline.

A research group (Rajiv Gandhi Institute of Chest Diseases, Bangalore) has studied the drug-resistance and treatment outcomes in the 224 confirmed MDR-PTB patients till 2010. They have reported that majority of patients are resistant against all four first-line drugs. However, others develop variable resistance against different drugs. Hence, the treatment pattern has to be decided based on the drug resistance.16

**Vaccine initiative**

Vijaya’s group (Indian Institute of Science, Bangalore) has explored a new promoter in the Mtb genome which functioned efficiently in E. coli to construct a vector. This has been used to drive expression of heterologous genes in Mtb and in Bacillus Calmette–Guerin (BCG) which can be a promising BCG-based multivalent vaccine. They have found antigens coded by several novel genes of Mtb that could elicit human T cell responses of the TH1 phenotype which enable protection against an experimental challenge in the guineapig animal model. These vaccine candidates are under clinical trials. They have used Green Fluorescent Protein-tagged genes inserted into the Mtb genome and monitored movement of these proteins inside the infected macrophages. Simultaneously, a group in Delhi University, South Campus has developed expression of Mtb antigens in BCG to develop candidate recombinant BCG vaccine (rBCG85C) and candidate DNA vaccine and evaluated them against aerosol infection of Mtb in guineapigs by heterologous prime boost approach15. These have been expressed sustained and better protection than BCG and recommended for human clinical trials. Also, they are engaged in identification, validation and application of new drug targets for TB as well as structure and function analysis of mycobacterial transcription signals and gene expression. A similar approach on rBCG85C bovine TB vaccine development has been carried out jointly with AIIMS and Biovet Pvt Ltd, Karnataka.

**Basic biology**

Nagaraja’s group (IISc, Bangalore) has done extensive work on mycobacterial DNA gyrase and topoisomerase I involved in regulating the super coiling events in the cells16. Balaji and group has studied the signalling mechanisms involved in macrophages/dendritic cells when infected with pathogenic mycobacteria. Different survival strategies exhibited by Mtb and also the PE/PEP family antigens of Mtb have been functionally characterized by him. A group led by Muniyappa has done several proteomics study on RuvAB proteins of Mtb; role of UvrD1 and UvrA proteins on suppression of DNA strand exchange, etc.

Studies are in progress at the Institute of Genomics and Integrated Biology, New Delhi on Chemical Biology of Mtb by exploiting the metabolic pathways and mechanisms involved which generates molecular diversity responsible for the virulence and pathogenicity of the bacteria. Rao and his group (ICGEB) have been experimenting the signal transduction pathway of Mtb, more so, the details of secreted antigen namely MTSA-10 modulating macrophage function by redox regulation of phosphatases. Analysis of genetic polymorphism from
Mtb isolates from patients of different geographic regions revealed that RD1 region is frequently present in Indian isolates and RD9 region is well conserved. These results indicated that Indian Mtb strains are more ancient. They have also studied molecular epidemiology of TB with the help of a systems biology approach. It is proven that when human being stay in long, frequent, or close contact with TB patients, they face a high risk of contracting the disease which has a 22% infection rate. Das et al. have recently demonstrated the survival of dormant Mtb in the CD271+/CD45– human bone marrow Mesenchymal Stem Cells in in vitro culture, both in mouse and a human model.

The National Tuberculosis Institute, Bangalore has worked on surveillance of drug resistance and TB control strategies in sync with regional and national programme delivery.

For a killer disease like TB, the pressure to treat as many people as possible, with limited resources is of prime importance. Though enough research has been done on TB, special efforts are still needed to make the DOTS program more successful. Multiple diagnostic samples loading, sophisticated imaging technologies and sample handling procedure, cost effective technologies, regulatory policies, etc. will definitely hasten up the process.

1. TB India 2011, RNTCP Annual Status Report, GoI.
16. http://mcbl.iisc.ernet.in/Welcome%20to%20MCBL/Faculty/Nagaraja/Nagaraja.htm

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