**Project title:** Combating Tuberculosis in the Region by development of Diagnostics and Drugs

**Project summary:**

A. **Diagnostics:**

One-third of the world's population get infected with *M. tuberculosis*, and new infections occur at a rate of one per second approximately. It ranks second most common cause in term of death by infectious disease after HIV. MTB is an airborne pathogen causing the TB disease by the droplet particles released to air when pulmonary TB patient coughs. Globally, especially in the entire six WHO region, the incidence rate of new TB cases has been falling over the last decade, achieving the MDG global target. However, the rate of decline of 2% per year needs to be leveraged to achieve the Stop TB elimination target. TB deaths each year, are partly due to late or missed diagnosis, hence, improving the performance (sensitivity and Specificity) of diagnostics and their availability are key to reduce global and regional morbidity and mortality. The delay in diseases detection is directly related to lack of availability of PoC diagnostics and drug resistance TB detection tool. The majority of the TB (60%) is detected at the peripheral health care setting emphasizing the need for PoC test.

In South East Asian regional countries, sputum smear microscopy is the most widely used diagnostic test; however it has low sensitivity and misses almost half of the pulmonary TB cases. Culture, which is the gold standard for drug sensitivity testing is not easily accessible as a tool for basic screening and diagnosis of DR TB cases. Hence, there is a real need for development and deployment of a Point of Care tests for TB, which can really be used at the peripheral health care system for testing the detection of MTB at PoC level and inclusion of drug resistance in the same sputum sample.

TB treatment initiation by the current drug regime need prolonged treatment by toxic drugs, thereby open the scope of non-compliance. Moreover, resistance arising to the major drugs to the first line of defence adds up the complexity. The only available BCG vaccine has several limitations and need replacement and modification. TB cannot be treated presumptively; a definitive diagnosis must be made before treatment initiation. Importantly, to address the unmet need of WHO Stop TB program and the Millennium Development Goal 6, an appropriate Point of Care diagnostic, which is currently unavailable, is needed for the countries in the South East Asia region which has huge burden of TB disease of all types (MTB, MDR, XDR).

The diagnostics for TB ranges from the conventional microscopy of sputum samples to new age Phage detection system, serodiagnostics, Nucleic Acid Amplification tests, Immunodiagnostics, Interferon Gamma Release Assay (IGRA), T spot TB test, Loop Mediated Isothermal Assay (LAMP) etc. The recently developed real time PCR based GeneXpert MTB test by Cepheid, USA has been evaluated in field conditions in India and the TB control programme is adapting this in large scale. However, the cost and the need for constant power supply have restricted its use as a truly PoC test for TB in India. Importantly, WHO’s negative policy on TB serodiagnostics, has discouraged the use of commercial serological tests for Tuberculosis, India has banned the use of these tests for TB diagnosis. There is advocacy for a robust, reliable, rapid, sputum based NAAT/ molecular test which has better sensitivity than smear microscopy and shows accuracy like Xpert MTB/Rif providing same day result and can be deployed at the peripheral microscopy centers in the SEA regional countries.
Objectives:

- To support and refine an indigenously developed chip based nucleic acid amplification technology for a point of care test to detect TB and to detect rifampicin resistance as a follow-on process, with the same elute from the earlier prepared sample.
- On confirmation of “proof of principle” to further support validation, demonstration studies for use under programme conditions as a PoC in the health system for rapid diagnosis of TB and rifampicin resistance.
- The test will be registered for use through the Drug Controller General India, (the Indian FDA counterpart) the regulatory authority for detection of TB. The test can potentially be deployed for validation for early diagnosis of MTB in the public sector. Validation through Indian centres of excellence in TB research like National Institute of Research in Tuberculosis, Chennai (NIRT), National Institute of Tuberculosis and Respiratory Diseases, New Delhi (NITRD), JALMA Institute of Leprosy and other Microbial agents, Agra (JALMA) etc. would create a body of data for the national programs consideration.
- The refinement for inclusion of rifampicin resistance detection is absolutely essential keeping in mind the prevalence of drug resistance in countries like India which accounts more than 80% of MDR TB in the SEA Region. At the global level Foundation of Innovative and New Diagnostics (FIND) will be contacted for multi-country studies in parallel.
- THSTI in coordination with ICMR could coordinate in county studies as detailed above. In addition, THSTI could leverage its resources to help improve the platform for development/validation of resistance, improvement in sample preparation and automation of sample to result platform to keep it constantly relevant.
- Funding could be leveraged for the above development.

Cartridge/chip based NAAT are promising for accuracy and speed of diagnosis due to the inherent technology safeguards, which prevent cross contamination and hence false positivity during the testing procedure. This project is looking for options for easy to use test refinement/ modification of the existing promising indigenous product targeted as PoC. This is a chip-based PCR test in the detection of MTB in clinical sputum specimens, run on a battery-operated, automated microPCR device with semi-automated sample processing which has shown sensitivity and specificity of more than 95% respectively. The preliminary study shows that the test allows detection of TB in approximately one hour.

However, the platform would benefit for increasing the ease of use at the Point of Care setting, such as:

a. Total automation of specimen processing
b. Inclusion of drug resistance platform
c. Creation of a sample to result system
d. Automated sample prep version and the integrated version need to undergo evaluation studies.
e. It is proposed that development and validation of this platform through the large evaluation study in India which can be extended to multicountry validation studies in other countries of SEAR would be done before the product can be deployed widely as a diagnostic test for TB at the peripheral level.
f. Inclusion of drug resistance platform in this and validation will help to introduce it at the referral level too. Hence, both the health care level will be taken care off.

The recent “Global Tuberculosis report, by WHO, 2013 has mentioned the possible approaches including the micro-PCR based system made in India as one of the promising lead candidate. However, has limited evaluation data from the country set up. The most important aspect for a product development is timely investment of finances to support the R&D for refinement and automation. Hence this project could be the path breaking innovative initiative for the development and use of a product that could be a cost effective, low touch PoC especially useful in high burden resource constrained countries like India, Indonesia etc.
B. Drugs:
Background: The medical need:

The need of new drugs for TB is recognized by experts around the world. Development of new drugs for TB has special relevance to the South Asia as the WHO SEA Region bears about 40% of the global burden of TB. The initiatives by the product development partnerships (PDP) like Global Alliance on Tuberculosis (TB Alliance), pharmaceutical companies like Janssen Pharmaceuticals, Otsuka Pharmaceuticals, Astra Zeneca, Pfizer, etc, have brought a pipeline TB drugs to the development phase of clinical trials. In December 2012, the U.S. Food and Drug Administration (FDA) approved Janssen’s drug Sirturo (bedaquiline) as part of combination therapy to treat adults with MDR TB when other alternatives are not available, in the United States. While the drug pipeline looks promising, very few institutions in SEA region have the capacity to participate in the drug development efforts, particularly clinical trials. In this situation, the drugs are getting developed in advanced markets and approved by agencies like FDA, while SEA region is lagging behind, limiting access to and causing delays for efficacious drugs to reach the deserving patients.

The proposal is to set up a drug development platform for TB in the countries with disease burden in collaboration with competent institutions in public and private sector in such countries. The most expensive and risky part of drug development process is conduct of clinical trials. Once such a platform is established the PDP organisations, public funded efforts and pharmaceutical companies working on discovering and developing drugs for TB will be able to conduct development studies of drugs in these countries. This is expected to make drugs available to the patients without much delay of its launch in advanced markets, making these drugs accessible to patients in need and affordable as the cost of development will be comparatively less in the developing world. This proposal is expected to derisk the drug development process to a large extent, improve the speed of introduction of the drugs into disease burden countries with the promise of affordability and accessibility.

The above approach is demonstrated through the proposed novel MDR regimen trial of OSDD of CSIR, funded by the Government of India.

The CSIR-OSDD programme has been able to put in place the necessary ingredients for clinical development as demonstrated below and this is a replicable model scalable to conduct clinical trials of a number of TB drugs in different countries.

The Concept:

MDR-TB treatment requires 24 months of a regimen that includes a Quinolone and an injectable along with 4 other drugs. The treatment is toxic and cumbersome leading to poor compliance and limited success. A novel well-defined single regimen with efficacious drugs that can shorten the duration of therapy is a dire and urgent requirement.

The treatment of Tuberculosis faces a new cliff, a cliff with several novel drugs in late stage clinical trials but with the danger of them being introduced one at a time into a failing regimen which would indeed be a rapid death knoll for the new drug. The need of the day is the development of novel regimens, which can be used for the treatment of drug sensitive (DS) and MDR TB. The current treatment of MDR-TB is a 24 month regimen consisting of Moxifloxacin + Levofloxacin + Pyrazinamide + injectable Aminoglycoside + Cycloserine + Ethionamide +/- Clofazamine.

The TB Alliance (a not for profit PDP) pioneered the concept of progressing novel regimens for TB through the development of a combination of PA-824+ Moxifloxacin + Pyrazinamide (PaMZ). This combination includes PA-824 which is a novel 'nitro imidazopyran' that has completed extensive Phase I
and Phase IIa trials on DS TB patients in South Africa and found to be efficacious and safe (multiple 14 day studies) in humans. Moxifloxacin and Pyrazinamide are currently in use for the treatment of MDR-TB.

The project approach and design:

The current design of the Phase IIb clinical trial entitled “A Phase II Open Label Randomised Clinical Trial to evaluate the anti bacterial activity, safety and tolerability of a combination of PA-824, moxifloxacin and pyrazinamide, or PA-824 when administered with the Category IV regimen of RNTCP in adults with newly diagnosed multi-drug resistant pulmonary TB. An 8-week study intends to evaluate the efficacy of the regimen on MDR patients along with studying the safety of the regimen over this period. This will be first major study of the regimen on MDR patients as most of the previous clinical studies with the regimen have been on DS patients.

The project design also includes the study of:

1. The pharmacokinetics of the drugs at various intervals of treatment to determine the exposure and metabolism in Indian patients.
2. Pharmacogenomic study: it is envisaged to sequence the genome of all the isolates, as well as determine the genomic status of the patients in terms of the known transporters and metabolizing enzymes.
3. It is envisaged to concomitantly study the ‘bacterial load’ as a prognostic marker using the newly developed diagnostic kits, Truescript by BigTec and that developed by Reametrix.

Current status of the clinical trial:

The study protocol has been finalized, applications seeking permission in the prescribed format submitted for clearance with the Drug Controller General of India (DCGI) and the final clearance is awaited.

Partnerships:

CSIR-OSDD has licensed the novel combination for developing, producing and marketing the product for India from TB Alliance.

The investigator hospital is NITRD, a public funded hospital under Ministry of Health.

The protocol and Trial designs were finalized by NIRT, Chennai, a research hospital under the ICMR.

CSIR-OSDD is the sponsor of the trials. OSDD has approached the Government of India for funds for the Phase IIb trial.

OSDD is also investing in one location to develop competence in conducting clinical trial. This location is a publicly funded hospital where infrastructure and competence is available, which needed to be fine tuned and topped up to meet the challenges of conducting clinical trials of internationally acceptable standards. This additional requirement is brought in by OSDD.

OSDD treats the drug development as a pre-competitive activity. OSDD is not expecting return on investment and will not charge any royalty from the manufacturers and will license the drug non-exclusively to facilitate generic manufacture and competition in the market place which will make the drugs affordable and accessible. The drug developed by OSDD will be available without royalty to the developing world. The reason for not charging royalty is multifold. It reduces ultimate cost of the drug. It
also factors in the fact that public funds have already been used for development of the drugs. In most developing countries TB drugs are administered through government agencies who are the purchaser of the drugs. Charging royalty on the drugs developed out of public funds which will be purchased by public exchequer will only be meaningless.

OSDD brought together a wide ranging group of expertise to conduct the proposed trials. The entire effort treats the drug development phase as a precompetitive collaborative phase. Once developed, the drug will be licensed to manufacture by generic manufacturers. This is a scalable and replicable model and any organization with the required competence can replace OSDD. If multiple facilities can be created and manpower trained for conduct of clinical trials, any new drug being brought to market can use this platform.

*As taken from original proposal template, question 5.

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