Meeting of the Federal Tuberculosis Task Force April 8, 2013, Bethesda Maryland

Science Track:

This breakout group was to inform participants about resources and programs available at the various USG agencies involved in TB R&D and to discuss whether these resources are optimally applied for TB product development.

The session was started with a presentation by Dr. Andrew Vernon (CDC) who summarized the current pipeline of TB drug candidates and ongoing and planned clinical trials, and gave an overview of ongoing collaborations and discussions among the various funders and stakeholders contributing to advanced clinical development of TB drugs. This presentation provided a framework for discussion about whether the available resources leveraged by USG partners are optimally used in TB product development.

One of the overarching question the group deliberated on was whether there are any obvious gaps in TB R&D that can only be (or are optimally) addressed by the USG since they are of low interest or priority for pharmaceutical companies, biotech, not-for profit organizations or academia. The group identified several areas of interest that should be explored within the Framework of the US TB Task Force.

1) **Maintain international capacity in biomedical research and clinical trials/studies for TB interventions.**
   While many organizations are using international collaborations for clinical TB research, many of these sites were established and are maintained through USG funding (NIH, USAID, CDC). Training of investigators, as well as funding of collaborative clinical activities has been a core contribution by the USG and needs to be maintained. A particular gap that was identified in discussion was to maintain staff and expertise during the time that elapses between clinical trials sponsored by product development entities. It was envisioned that supporting studies/trials to study existing interventions may be able to bridge the gap between regulatory trials and also produce much needed medical evidence for the current guidelines/recommendations for use of first and second line drug regimens for TB. For this, better in-country education on the importance of scientific studies to help guide treatment recommendations is needed. Often local health departments and IRBs are familiar with the need for registration trials for new entities but are not aware of the need to create better medical evidence for existing interventions and strategies that are the subject of global TB program recommendations.
   - NIAID representatives (NIAID is the lead institute for TB at NIH) indicated that NIAID is planning on revitalizing its NIH wide TB working group to inform about each Institute/Center's activities in TB and/or identify technologies and approaches used in other fields that may be of benefit for TB. NIAID/DMID will organize these meetings.
   - NIAID/CDC is holding weekly conference calls to inform of each other's activities and will explore expanding these calls to include other USG organizations/NIH Institutes to broaden collaborative efforts.

2) **All aspects of pediatric TB care and diagnosis are likely best served through USG involvement.** Pediatric TB, while of significant importance for individual patients and their families is not considered a driver or major contributor to the spread of TB and has therefore not received much public health attention. Therefore, treatment, prevention and diagnostic strategies for pediatric TB are poorly developed, are based on adult care recommendations and need to be evaluated and adapted for this particular population. Few funding organizations are motivated to undertake dedicated studies in pediatric patients to contribute to tailored care and treatment recommendations and USG contributions (NIH, USAID, CDC, etc.) will remain important in this area.
    - The NIH wide TB working group (see 1.) will address needs and opportunities in pediatric TB in consultation with outside organizations where appropriate.

3) **Migration of available clinical trials data into public use formats.**
A significant body or safety and "efficacy" data exist for current and experimental new TB drugs, vaccines and diagnostics. To facilitate cross cutting evaluation of these data and provide information to drug developers to facilitate clinical trial designs and regulatory submissions (using existing data as baselines to justify safety and or efficacy endpoints) and post-marketing surveillance, existing data should be transitioned into common formats and databases. While data standardization efforts have been initiated for TB trials, there is not yet clear consensus on many definitions. However the group felt that initially transferring available data into CDISK formats may be a reasonable step and allow targeted discussions around data standardization. Experience from the HIV/AIDS field showed that before large data standardization efforts and discussions are undertaken, it is useful to define a case or specific question that can be addressed through consolidation of existing data first, rather than standardizing data and then defining their use afterwards.
    - The group agreed to establish a small discussion group to explore questions that would benefit from standardized, cross cutting data evaluation and then based on these questions, define what processes may be required to merge datasets from available databases.

At the end of this breakout session, the various agencies present were asked to identify what they would consider relevant, USG mission relevant gaps in TB R&D that may be addressed through the US Federal TB Task Force. Of particular interest was a focus on studies that the Pharmaceutical Industry and or PDPs find discouraging or too difficult to undertake and that have been shown to contribute to barriers for effective product development in TB

1) Increase commercial interest for Rifapentin to encourage further development.
    a. If medical evidence for the use of Rifapentin in the treatment of latent TB infection (LTBI) could be obtained, Rifapentin could be recommended for LTBI treatment and would create a significant US or global market for the drug.
2) Create medical evidence for the utility of other licensed antibiotics that are currently used off-label in the treatment of TB
    a. This would increase confidence in the safety and efficacy (and create market potential) or use of available interventions and might encourage label expansion particularly for generic, affordable drugs.

3) Create monitoring and evaluations systems for the global use of GenExpert Mtb/Rif.
    a. The WHO has endorsed the use of this technology for diagnosis of TB and MDR-TB which has resulted in many countries acquiring this diagnostic for TB control efforts. However, a strategic approach to monitor its effectiveness and optimal use has yet to be developed. The USG could lend expertise and guidance for the development of these monitoring approaches through the international working group of the Federal TB Task Force.
4) Coordinate efforts for the introduction of new TB regimens into global use
    a. The WHO is convening stakeholders to establish a guiding framework for the introduction of new drugs licensed for TB treatment (currently focused on the introduction of Bedaquiline as part of second line therapy). Within the USG, efforts and trials to create medical evidence for the use of new drugs in TB treatment should be coordinated to assure consisted approaches and data standards are used. The Federal TB Task Force could create a working group to discuss integrated approaches.
5) New or repurposed drugs for use in TB drugs have to be evaluated in "high-risk" populations, such as pregnant women and children.
    a. These studies require significant expertise, infrastructure and educated volunteer populations and are therefore not easily or willingly undertaken by drug developers. The USG through its various organizations, particularly at NIH, can provide significant contributions to this area.
6) Increase investigator training efforts for TB
    a. To maintain a solid and self-sustaining base of well-trained clinical and biomedical researchers in TB in endemic countries, USG should more proactively identify opportunities for collaboration between US/endemic country scientists and consult for the establishment of local training programs. The NIH wide TB working group can contribute to these efforts.
7) Develop reliable capacity and assays for "3rd line" TB drugs
    a. Depending on the availability and tolerability of recommended second line drugs, TB care programs frequently include what are considered 3rd line drugs. However, no reliable diagnostic tests and assays are available that allow for evaluation of resistance against these drugs. While momentum has been created through the US Federal TB Task Force's Working group on Diagnostics to improve reliability of second line drug susceptibility testing (DST), 3rd line DST remains under resourced.
8) Improve PK/PD modeling efforts to contribute to proper use of 2nd and 3rd line TB regimens while new chemical entities are being developed.
    a. Current treatment recommendations for MDR TB continue to rely on expert opinion with few randomized clinical trial data available to guide optimal use. Considering the cost of MDR TB treatment trials and the limited availability of experienced trial sites, hypotheses for dosing optimization could be generated through PK/PD modeling and be the basis of targeted, high impact randomized controlled trials.
9) Develop strategies for treatment of suspected drug resistant latent TB infection.
    a. This approach will require detailed in depth discussions among epidemiologists, control program experts and biomedical researchers within the Federal TB Task force and international agencies.