THE 3P PROJECT. Better TB treatment. Faster.

A solution to accelerate innovation and collaboration to achieve a one-month TB regimen accessible and affordable for all

WHY THE 3P PROJECT FOR TUBERCULOSIS IS NEEDED

Tuberculosis (TB) is the world's deadliest infectious disease: in 2015, 10.4 million people fell ill with TB; 1.8 million died. Many TB strains are difficult or impossible to cure with existing drugs. In 2015, nearly 600,000 people were diagnosed with DR-TB, 200,000 died. The recent UN declaration on antimicrobial resistance (AMR) named TB as a disease of importance when addressing global antimicrobial resistance and it is predicted that 75 million people will die from TB by 2050, unless better treatments become available.

TB requires long treatment, 6 months for drug-sensitive TB, and the current standard of care for DR-TB is up to two years of treatment. This include at least six months of painful daily injections and 15,000 tablets with terrible side effects such as deafness, psychosis and severe nausea, with only a 50% cure rate. There have been some recent advances in DR-TB treatment with guidance given on a shorter regimen of nine months for those with less severe forms of DR-TB and clinical trials looking at a six month treatments for DR-TB.

These developments offer some hope for patients with drug resistant forms of TB but the ultimate goal in TB treatment is the development of a short pan TB regimen – a one month or less treatment combinations to effectively, safely, quickly, affordably and simply treat all forms of TB for everyone. In the immediate term there is an urgent need to improve the treatment for DR-TB. In order for these new treatment combinations to be developed the status quo must be transformed to deliver:

- **a healthy TB drug pipeline** with a number of compounds in all phases of development. The pipeline for new TB drugs is weak; there are only 6 new chemical entities in clinical development. This is unlikely to be sufficient to achieve the goal of a one month pan-TB regimen.
- **an increase in investment;** the current spending of $620 million on all TB R&D (vaccines, diagnostics and treatment) is only third of the $2 billion annual funding target outlined in the 2011–2015 WHO Global Plan. Funding in TB drug R&D is only 28% of the $810 million called for in the Global Plan.
- **an open collaborative R&D approach** that reduces risks and costs associated with testing multiple drugs for combination treatments by incentivizing research organizations to share compounds, scientific data, clinical trial results as early as possible and to conduct medically appropriate research on combinations of compounds.
- **a de-linking of R&D cost from prices to ensure affordability and access of resulting treatment regimen**

SUMMARY OF THE 3P PROJECT

The **3P Project** aims to rapidly deliver affordable, effective shorter regimens for TB through an open collaborative approach to conducting drug development and through novel approaches to financing and coordinating R&D. The 3P Project implements three mechanisms to facilitate the necessary and appropriate R&D for TB regimens:

- **Pull** funding to incentivise R&D activities through the promise of financial rewards (milestone prize) on the achievement of Investigational New Drug approval[1]
- **Pooling** of intellectual property (IP) and data to ensure open collaborative research and fair licensing for competitive production of the final products
- **Push** funding to finance R&D activities upfront (i.e. through grants)

BACKGROUND: WHY IS TB DRUG R&D FAILING TB PATIENTS?

FOCUS ON DEVELOPMENT OF SINGLE DRUGS, NOT NEW REGIMENS. In 2012, the first new TB drug in 50 years received accelerated approval for use in treating MDR-TB, and a second new drug was approved in late 2013. Unfortunately these two new drugs have not resulted in any improvement in the duration or side effects of the current DR-TB treatment. As TB must be treated with a combination of drugs one new drug on is not enough. The lack of collaboration and transparency means that clinical trials to test these two new drugs in combination in order to ensure they can be safely combined and then to build a new, shorter, better regimen will not be completed for several years. Many organisations working in the area of regimen development, including TB Alliance and the UK's Medical

[1] If product fulfils a Target Product Profile and shares IP and Data.

Research Council (MRC) have encountered obstacles in accessing new drug compounds for testing as part of improved treatment regimens. There is currently no IP licensing mechanism linked to financial incentives – either grants or prizes - to incentivize the collaborative, open research needed to stimulate regimen-based R&D activities.

INADEQUATE FINANCIAL INCENTIVES FOR COMPANIES. The market for TB regimens is far less lucrative than for other diseases and is marked by chronic underinvestment; this translates into slow or stalled scientific progress, as promising drug candidates languish for lack of a business case. Private-sector investment in TB R&D has fallen by a third since 2011, and since 2012 Pfizer, AstraZeneca, Novartis and Vertex have all withdrawn from TB drug development, closing R&D facilities. The lack of market incentives makes it difficult for research organizations to enter the TB R&D field and to take TB drug candidates through to late-stage clinical research, leaving significant gaps in the pipeline: there are only 2 new TB drug candidates in phase one clinical development. Many of the compounds currently in Phase II and Phase III are older "repurposed' compounds that don't represent investments by commercial developers. With the exception of Pretomanid, new drugs are currently being developed as single products and are not involved in combination trials or new regimen trials until after receiving regulatory approval.

LACK OF FINANCIAL SUPPORT TO PROGRESS PRECLINICAL COMPOUNDS. In early-stage and preclinical research, the majority of TB compounds are being developed by public institutions, small companies or product development partnerships (PDPs), and it is unclear if they have the necessary capital and resources to bring an adequate number of new products forward to later clinical trials. For example preclinical development of the new drug candidate PBTZ169 was funded by the European Commission, but further progression of this potential new chemical entity to clinical trials stalled as there were no dedicated funding streams available for the next stage of development.

ACCESS AND AFFORDABILITY NOT GUARANTEED: When new TB products come to market, they may not be affordable or accessible in countries where the disease burden is highest. For example, the new TB drug Bedaquiline cost US$900 in low-income countries and US$3,000 in middle-income countries for a 6-month regimen, until it was made available through a donation programme and Delamanid is priced at US$1,700 in Global Fund eligible countries, and this is on top of the cost of several other drugs that need to be added to the regimen.

A JOINT POOLING & FUNDING MECHANISM TO PROMOTE INNOVATION AND ACCESS

The 3P Project is a new way of doing research and development to ensure that researchers are rewarded for investing in TB research and development and that the system promotes regimen development and clearly states the research priorities. It does this by creating a new open collaborative framework for regimen development based on the sharing of data, the pooling of intellectual property and compounds and adequate and timely incentives for multiple actors to enter the R&D process in order to accelerate drug regimen development timelines.

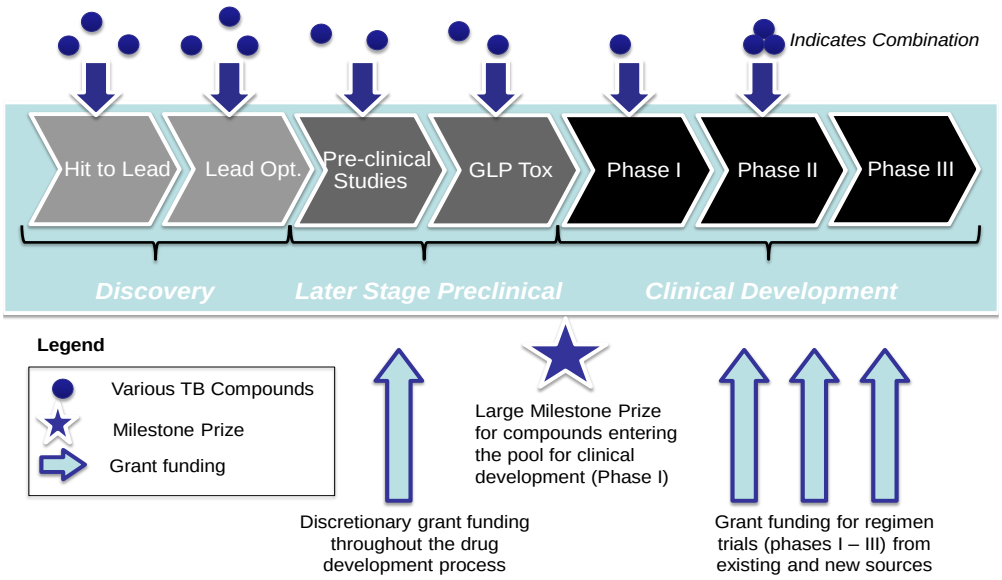
By offering a reward (prize) for appropriate compounds/drugs moving from preclinical development to clinical trials and promoting collaboration for drug combinations and regimen development, it will allow drug-drug interaction and potential beneficial drug combinations to be discovered and accelerate the development of new regimens. The increased investment and structuring of funding through both prizes and grants (push and pull mechanisms) will dramatically increase the number of compounds in the clinical development pipeline, enhancing the work of PDPs such as the TB Alliance, and other developers in designing and testing regimens working towards to ultimate aim of a one month or less treatment for all forms of TB. There is potential for re-purposed compounds and those further down the pipeline to enter into the 3P Project open collaborative framework.

In order to ensure affordability of the final medicines, the 3P Project separates (or "de-links") the cost of R&D from the price of the resulting treatments. Once a regimen receives regulatory approval, the individual drugs or fixed-dose combinations could be licensed to multiple manufacturers with proven capacity to produce quality-assured drugs through the patent pool, allowing competition to lower prices to a sustainable level. Regimen prices would be determined independent of the cost of R&D. This 'de-linkage' also facilitates stewardship of the end regimen by removing the need to market the product to recoup R&D costs within the life of the patent as well as building good stewardship practises into the licences.

CONCLUSION: The 3P Project proposal offers benefits over the current TB R&D framework by:

- Reducing duplication of research efforts, thereby saving time and money
- Reducing the risks by developing potential combinations early in the R&D process
- Accelerating the development of all-new drug regimens
- Reducing the risk of resistance to new compounds by ensuring their use as part of regimens
- Coordinating sources of funding and linking financial rewards to an obligation to share scientific and clinical data and Intellectual Property Rights Separating ("de-linking") R&D costs from the final price of TB combination regimens
- Represents a practical solution to a key part of the AMR response with TB expected to cause one in four deaths due to AMR.

Schematic representation of the proposed mechanism including prizes, grants and patent pooling:



How it works: