

New Report by Doctors Without Borders/Médecins Sans Frontières (MSF):

DEVELOPMENT OF NEW DRUGS FOR TB CHEMOTHERAPY:

Analysis of the current drug pipeline

Overview:

The standard TB treatment available today is long and complex. It relies on drugs developed over forty years ago and takes six months for patients to complete. The last four decades have brought nothing in the way of improvement.

Yet after this standstill, alternative models of drug development have recently emerged and are making inroads into improving TB treatment. Some companies have also re-engaged in this field. But it is questionable whether the efforts currently underway will be enough to provide a revolution in TB treatment that will be needed in the long term to put an end to the toll the disease takes. Dramatically reining in TB will take much greater investment to ensure that the expanded knowledge of basic TB science is seen through to new drug development.

A Fuller Drug Pipeline, But Will it be Enough?

Thanks to alternative research and development (R&D) models, compared to just five years ago, the TB drug pipeline contains several promising compounds. The TB Alliance, a product development partnership (PDP) funded mainly by the Bill & Melinda Gates Foundation, has played an important role in this, and is associated with roughly half of the drug compounds in the pipeline today.

At the same time, increased public awareness about the lack of R&D for diseases that primarily affect developing countries has prompted some pharmaceutical companies to carry out TB drug R&D on a 'no-profit-no-loss' basis, and three companies are conducting R&D for TB on a commercial basis. Some first steps in the right direction have thus been taken, with hopes that drugs such as moxifloxacin, an existing antibiotic, can provide shortened TB treatment, down from six to four months, by 2010.

Yet although these initiatives are encouraging and have shown that it is possible to make advances on TB drug development, the current efforts are not enough to result in the radical improvements, such as shortening treatment to a few weeks or even days, that will be needed to make TB controllable.

First, there are simply not enough promising compounds in the drug pipeline, compared to pipelines for other diseases that predominantly affect wealthy countries. This significantly reduces the likelihood of developing an entirely new treatment combination.

Second, many of the compounds in the pipeline today are derivatives of existing ones, or work in a similar way to drugs that are used to treat TB today. While this is the quickest way to bring new drugs to TB, it also increases the risk of cross-resistance problems, thereby rendering drugs ineffective.

Further, PDPs like the TB Alliance face serious funding gaps when it comes to moving candidate compounds into the expensive clinical trial phase. Most of the funding to neglected disease R&D is still philanthropic, with governments only contributing 16% to drug development PDPs in 2005.

Translational Research: From Basic Science to Drugs

Despite movement on various fronts, one crucial problem in the field of TB is that the advanced knowledge about the bacterium that causes the illness is not translated into targets that can be used for screening new potential drug compounds. The major bodies that fund TB research have typically invested in basic research projects and 'hypothesis-driven' science,

GENEVA 30 OCTOBER 2006

and academic laboratories struggle to find the funds for projects that fall between basic and applied research, creating a critical funding gap.

For diseases that affect wealthy countries, such as cancer or heart disease, drug companies actively scout out advances in basic science with potentially lucrative drug targets in mind. But not so with TB, where most companies are more risk averse, and only embark upon projects once lead compounds have already been identified.

As the TB Alliance has very limited capacity to enter into the realm of this so-called translational research, the academic sector needs to push beyond the 'proof of principle' that it traditionally sees as its endpoint. For this to happen, there needs to be focused funding targeted at such translational research projects, seeing basic scientific discoveries through to concrete drug development. This funding needs to come from the public sector. Without this, the PDP model and current industry efforts will not be able to provide the real breakthroughs that are needed, now that all the low-hanging fruit has been picked.

In order for there to be a future with TB treatment as short as a few weeks or even days, governments will have to commit to bridging the gaps between science and drugs and support the necessary clinical development of already identified new compounds.

Discussion and conclusions (excerpt from MSF report: Development of New Drugs for TB Chemotherapy – Chapter 6)

As new models of drug development are being established, major advances have been achieved in the basic research field. Modern molecular and genetic tools have become available for *M. tuberculosis* (i.e. targeted mutagenesis, array-based analysis of mutant libraries, techniques for conditional gene silencing) and this has led to impressive improvements in the knowledge and understanding of the fundamental biology and physiology of *M. Tuberculosis* (Jansen and Yu, 2006; Kana and Mizrahi, 2004; Kaufmann et al., 2005; please refer to Appendix A for a detailed review of major advances achieved in the basic research field). This was made possible by funding programs supportive for research on *M. tuberculosis* lunched by major research funding organisms (NIH/NIAID, Wellcome Trust, EU) during the 1990s. However, as testified by the academic community, the situation is changing again and there are serious concerns that such a sustained funding availability will not last for long.

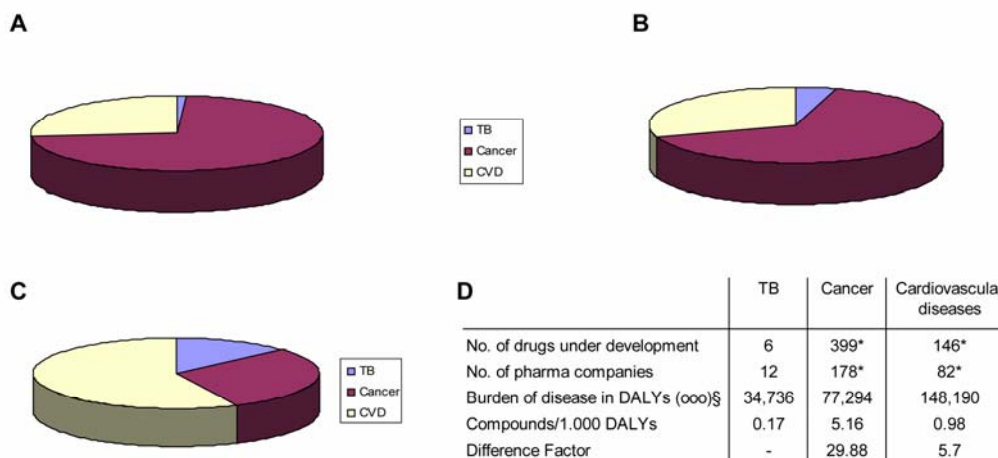
Today the TB drug pipeline is richer than it has been in the last forty years. This is also thanks to the work carried-out by the Global Alliance for TB Drug Development which is associated with approximately half of all compounds (or projects aimed to identify candidate compounds) currently being developed. Increased public awareness on the lack of R&D for neglected diseases in recent years has also led some multinational pharmaceutical companies to invest in TB drug development on a ‘no-profit-no-loss’ basis (namely, Novartis, AstraZeneca and GlaxoSmithKline). Some pharmaceutical companies have engaged in tuberculosis R&D on a commercial basis, and with some success: three of the six anti-TB candidate drugs currently in clinical trials have been developed for profit.

Pressing needs still remain

Despite the positive changes occurred in the last years, there are still problems that need to be tackled and major roadblocks still exist that are hindering the implementation of rational drug design and a fast progress in anti-TB drug R&D.

A first important question is if there are enough promising compounds in the TB pipeline for a comprehensive new TB treatment to be developed (Glickman et al., 2006). Although different attrition rates might apply, the number of candidate compounds is still small if compared to drug pipeline for diseases that principally affects wealthy countries. This is reflected by the limited number of biotech and pharmaceutical companies working on TB (see Figure 3). The ambition of the TB Alliance and its partners is to register an improved, faster acting regimen by 2010 and a regimen containing completely novel drugs by 2015 (TB Alliance Annual report 2004-2005

http://www.tballiance.org/downloads/2005%20annual%20008_6b.pdf). It is not possible to say today if the current pipeline will permit the attainment of this goal.



Another important issue concerns characteristics of candidate compounds currently in development. Table 4 summarizes the main properties in terms of mechanism of action of the candidate drugs that are in the pipeline (for more detailed information on single compounds see also table 3).

It is evident that many of the candidate drugs are either derivatives of existing compounds or target the same cellular processes as drugs currently in use. While analogs and derivatives are far quicker to develop, agents identified by this approach may have cross-resistance problem, as seen for the new rifamycins or quinolones (Ginsburg et al., 2003a; Moghazeh et al., 1996).

Fresh approaches and novel sets of microbial targets need to be taken in consideration. One example of a promising new compound is diarylquinoline TMC-207 (currently in phase IIa clinical trials) which acts through a novel molecular mechanism, most probably by inhibiting the ATPase synthase, leading to ATP depletion and pH imbalance. Preliminary results in animal models indicate that it has the potential to shorten the treatment to 2 months (Andries et al., 2005).

What also comes to light from a critical analysis of the drug pipeline is that rational approaches are weakly implemented in anti-TB drug discovery and development. Even the most promising novel drug candidates currently in clinical stage were identified serendipitously in screenings that were not designed originally for activity against *M. tuberculosis*. Moreover these compounds were selected for their ability to kill actively growing bacteria (Andries et al., 2005; Stover et al., 2000). There is consensus among the TB community that in order to obtain a real breakthrough in TB therapy and drastically shorten the treatment, there is an urgent need to identify compounds acting on key targets that are essential for mycobacterial persistence. There is a growing awareness that different subpopulations of bacteria that vary for their metabolism and growing rate can co-exist in an infected patient. Novel and more effective drugs should be rationally designed to interfere with metabolic and physiological strategies used by the bacteria to survive to host immune defences. An example is the search for inhibitors of the isocitrate lyase, an enzyme that has been proven to be involved in the “dormancy” response: compounds able to inhibit this enzyme are expected to kill persistent bacteria. However, most of the compounds in the current pipeline target actively growing bacteria and so have bactericidal but not sterilizing activity. Therefore, while drugs currently in the pipeline could significantly shorten the treatment to two to three months they are unlikely to lead to a major breakthrough and reduce the treatment to a matter of weeks or days.

Discovery		Preclinical	Clinical Testing
Thiolactamycin Analogs NIAID, NIH	Nitrofuranylamides NIAID, University of Tennessee	Diamine SQ 109 Sequella Inc.	Diaryloquinoline TMC207 Johnson & Johnson
Cell Wall Inhibitors Colorado State University, NIAID	Nitroimidazole Analogs NIAID, Novartis Institute for Tropical Diseases, TB Alliance, University of Auckland	Dipiperidines (SQ 609) Sequella Inc.	Gatifloxacin OFLOTUB Consortium, Lupin NIAID TBRU, Tuberculosis Research Centre WHO TDR
Dihydrolypoamide Acyltransferase Inhibitors Cornell University, NIAID	Focused Screening GlaxoSmithKline, TB Alliance	Nitroimidazo oxazole Back-up Otsuka	Moxifloxacin Bayer Pharmaceuticals, CDC TBTC, Johns Hopkins University, NIAID TBRU, TB Alliance
InhA Inhibitors GlaxoSmithKline, TB Alliance	Picolinamide Imidazoles NIAID, TAACF	Synthase Inhibitor FAS20013 FASgen Inc.	Nitroimidazole PA-824 Chiron Corporation, TB Alliance
Isocitrate Lyase Inhibitors (ICL) GlaxoSmithKline, TB Alliance	Pleuromutilins GlaxoSmithKline, TB Alliance	Translocase I Inhibitors Sequella Inc., Sankyo	Nitroimidazo - oxazole OPC67683 Otsuka
Macrolides TB Alliance, University of Illinois at Chicago	Quinolones KRICI, Yonsei University, NIAID, TAACF, TB Alliance		Pyrrrole LL 3858 Lupin Limited
Methyltransferase Inhibitors Anacor Pharmaceuticals	Screening and Target Identification AstraZeneca		
Natural Products Exploration BIOTEC, California State University, ITR, NIAID, TAACF, University of Auckland			







 Novel compound new mechanism of action	 Novel compound old mechanism of action
 Novel compound unknown mechanism of action	 Analogs and derivatives of existing compound
 Screening	 No info available

Table 4. Adapted from STOP TB Working Group on New drugs. Compounds have been categorized by the author considering their novelty in structure and mechanism of action

A critical obstacle to such rational design is the lack of a comprehensive characterization of the fundamental biology of mycobacteria as they persist in human tissues. Thus, the identification and validation of potential targets that are relevant for the survival of the bacteria *in vivo* still represent a difficult task. This high degree of uncertainty about biochemical processes and molecular targets that can be potential target for effective new drugs renders the whole drug R&D process risky and, therefore, even less attractive for pharma investments. There is urgent need for a better characterization of heterogeneity of TB lesions to obtain a clearer picture of the different microenvironments in which *M. tuberculosis* persists. Moreover, there is still a pressing need to decrease the degree of uncertainty about the critical metabolic processes that drugs should target to achieve sterile mycobacterial elimination. As part of the Grand Challenges in Global Health initiative (<http://www.gcgh.org/subcontent.aspx?SecID=403>) the Bill and Melinda Gates Foundation (Gates Foundation) is funding research into the molecular pathways of persistence, aimed at identifying novel targets and subsequently run target-based drug discovery programs.

A second critical obstacle to the implementation of rational drug design is the lack of well-validated drug targets. The fundamental genetics of *M. tuberculosis* growth and persistence in animal models are slowly being unravelled. Several enzymes involved in alternative metabolic pathways, energy generation, micronutrient acquisition, and survival in activated macrophages as well as in patient lesions have recently been identified as new sets of potential anti-microbial targets (Shi et al., 2005; Darwin et al., 2003; Sasseti et al., 2003; Schnappinger et al., 2003; Rachman et al., 2006), but validation of these potential targets through genetic or chemical inactivation is largely missing. This creates a critical gap in early stage drug discovery research (figure 4). There is an urgent need to translate this advanced knowledge about *M. tuberculosis* metabolism and physiology into validated targets that can be used for screening of new lead compounds. A key difficulty lies in securing sustained funding for research projects that fall into the area of target validation and chemical genetics.

The Gates Foundation recently announced a new initiative that specifically aims at accelerating drug discovery for tuberculosis). While acknowledging these important contributions, it must be questioned whether the isolated effort of the Gates Foundation will

GENEVA 30 OCTOBER 2006

be sufficient to promptly address such a broad and important public health problem. Much greater public leadership is needed.

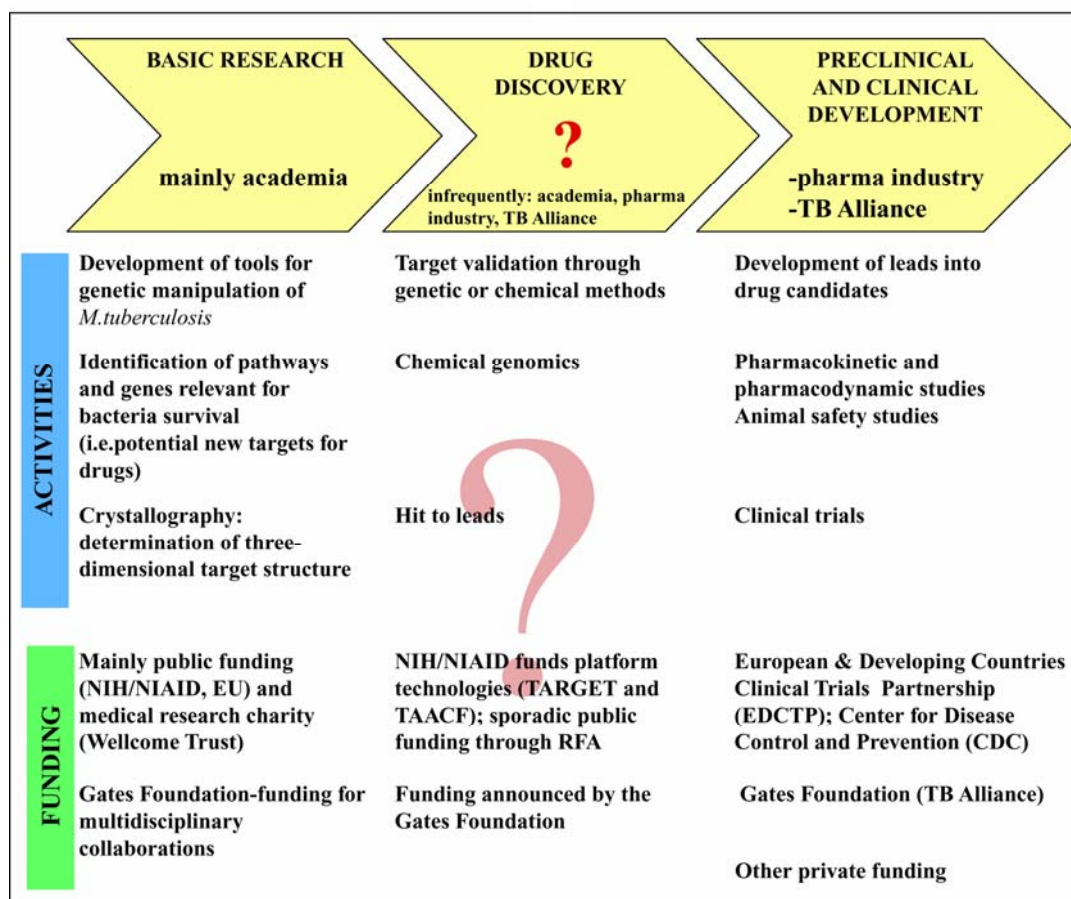


Figure 4. Main players in the anti-TB drug discovery and development process

Time to sow new seeds now as all the low-hanging fruit have been eaten

The product-development partnership (PDP) model has considerably contributed to a burst of activities in R&D for TB and other neglected diseases (Moran et al., 2005), mainly by testing and reformulating existing drugs already used for other indications and pushing into pre-clinical and clinical development existing drug leads that would have been otherwise forgotten in laboratory drawers for lack of an industry sponsor. Since improved therapies are urgently required the strategy of adopting a development-oriented portfolio has probably been a sensible short-term perspective. The critical question is whether this strategy will be successful in the long run. There are concerns that most of the “low-hanging fruit” have been already used up, and real breakthroughs will require a strengthening of early-stage discovery research to identify new compounds and targets. Without a thriving background of discovery-oriented translational research, itself largely dependent on public funding, the PDP model is destined to fail in a longer-term perspective. The renewed and welcome engagement of some pharmaceutical companies in TB drug development is so far still too modest and risk (cost) averse to tackle this problem.

Another point that deserves attention is the lack of rational approaches in the discovery process of compounds currently being developed. Serendipity will only get us so far. In the market-driven pharmaceutical sector, advances in genomic technologies, high-throughput screenings and X-ray crystallography are facilitating both the understanding of infectious organisms and approaches to rational drug design. These technologies need to be urgently and more comprehensively applied to neglected diseases if the pipeline for drug discovery and development is to remain full of real promise. The reluctance of the pharmaceutical sector to invest in early-stage discovery research for neglected diseases is leaving the pressing need to

GENEVA 30 OCTOBER 2006

translate basic scientific knowledge into novel targets and new therapies unmet. It is necessary to re-think the traditional roles played by academia and pharmaceutical industry in drug discovery and development when it comes to drugs for diseases like TB that do not represent an interesting market for the multinational pharmaceutical industry. Without proper public sector engagement into translational research and implementation of rational drug design, fast progresses will be severely hampered.