THE DEVELOPMENT OF NEW TUBERCULOSTATICS
ADDRESSING THE RETURN OF TUBERCULOSIS:
CURRENT STATUS AND TRENDS
(REVIEW)

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INTRODUCTION

Tuberculosis (TB) is acknowledged today as a global health catastrophe. In 1993, 111 years after Robert Koch’s discovery of the tubercle bacilli in 1882, the WHO declares TB “a global emergency” and compares it to a hypothetic third world war. In 2009, TB continues to kill 1.8 million every year and 5,000 people every day; that is one person every 20 seconds. Clearly, this shows the urgent need to improve treatment by either enhancing the application of existing agents or introducing new drugs. Such new agents should reduce treatment duration, have an acceptable tolerability profile, be active against MDR/XDR-TB, be of use in HIV co-infected patients, be active against latent TB. The focus of this review is to consider the challenges in developing new anti-TB drugs, to present an up-to-date and critical evaluation of the current therapy status and the progress of development of new agents in the phase of clinical testing as one of the strategies for improvement of TB treatment.

Keywords: Tuberculosis, drugs, current status, new tuberculostatics.

INTRODUCTION

Tuberculosis: A disease of poverty or result of malign human intent

Tuberculosis or TB is a common and often deadly infectious disease caused by various strains of mycobacteria, usually Mycobacterium tuberculosis. Tuberculosis usually attacks the lungs but can also affect other parts of the body. It is spread through the air. Most infections in humans result in an asymptomatic, latent infection, and about one in ten latent infections eventually progresses to active disease. New infections caused by M. tuberculosis are registered to occur at a rate of about one per second [1].

Tuberculosis have been considered to be a disease of poverty for many years with quite rare occurrence in the developed countries. Unfortunately recently more people in the developed world are contracting tuberculosis because their immune systems are compromised by immunosuppressive drugs, substance abuse, or AIDS. Several decades ago effective anti-TB drugs have been launched and one could hardly find a TB case to be demonstrated at the medicinal universities. But TB stroke back [2]! The return of tuberculosis was declared by World Health Organization (WHO) as a global emergency compared to a hypothetic third world war with 9 million new TB cases and 2 million deaths reported each year [3,4]; about one-third of the world’s population is already infected with M. tuberculosis [5].

According to the 13th annual tuberculosis report of the World Health Organization (WHO) published on World TB Day, March 24, 2009 - there were an estimated 9.27 million new cases of tuberculosis worldwide. Although this figure represents an increase
from 9.24 million in 2006, the world population has also grown, making the number of cases per capita a more useful measure of the problem [2].

In addition to this frightening statistics, resistant TB starts to develop. It is not a result of catastrophic natural forces such as earthquakes, tsunamis and hurricanes. It is not caused by malign human intent, as are terrorism and war, nor is it fostered by a dysfunctional relationship with the animal kingdom as are severe acute respiratory syndrome (SARS) and avian influenza [6]. It occurs in the presence of partially suppressive drug concentrations that enable replication of bacteria, formation of mutants, and overgrowth of wild-type strains by mutants. The emerged resistance is known as: Multidrug resistant tuberculosis (MDR-TB) – expressed as resistance to at least Rifampin and/or Isoniazid – the two most frequently used anti-tuberculosis agents, and Extensively drug resistant tuberculosis (XDR-TB) – consistent of MDR plus resistance to fluoroquinolones and aminoglycozides and/or other so called Second line agents discussed below. XDR-TB strains are established to arise in discrete stages by acquisition of drug resistance mutations within 7 years and the evolutionary path can occur in many strain backgrounds [7, 8]. According to some recent reports an increase of up to 500,000 new cases of Multidrug resistant TB (MDR-TB) and 40,000 new cases of Extensively drug resistant TB (XDR-TB) could be expected. As disturbing as these incidence figures are, they may be significantly underestimated [8].

The progressive worsening of resistance of TB to pharmacotherapy defines the attempt to fight tuberculosis without medication – the so called dawn of post-antibiotic age. The combination of high rates of TB infection with high seropositivity rates for HIV adds new levels of complexity to diagnosis and treatment [6].

The main issue, affecting the collective response to this deadly disease is entirely ethical and completely in the hands of the communities around the world. The efforts made against the return of tuberculosis and emergence of drug resistance defines the global attitude to its most disadvantageous members [6].

Through the past few decades, a large number of data have been generated, from the research performed in various aspects of tuberculosis. Interdisciplinary approaches and methods have been applied, in an attempt to improve the understanding of epidemiology and organism-host interactions. Development of new TB drugs and vaccines, implementation of newer therapeutic regimens, clinical management schedules for HIV uninfected and HIV co-infected patients are only some of the mechanisms used nowadays to help the fight against tuberculosis. TB control programs around the world are faced with Multidrug resistant (MDR) and Extensively drug resistant (XDR) tuberculosis, which are difficult and expensive to treat, and therefore threatening for the success of the current efforts to suppress the distribution of this deadly disease [9]. According to some recent reports, the application of aggressive treatment seems to be successful, but extremely expensive and unaffordable for some countries. For this purpose some structural and political changes are needed, so that enough resources could be separated for prevention and treatment of XDR-TB [6].

The present review offers a critical overview of the current anti-TB drugs arsenal and of the contemporary trends in the development of new tuberuostatics capable to overcome the bacterial resistance, especially of new agents being in progress in the phase of clinical testing. Some own investigations at a relatively early stage are also summarized. The serious problems related to the anti-tuberculosis drug therapy besides the other medicinal approaches to fight the disease are used as a background.

CURRENT ANTI-TUBERCULOSIS DRUG THERAPY AND ITS PROBLEMS

There are several major problems associated with the currently available TB treatment:

- The duration and complexity often resulting in nonadherence and leading to emergence of resistance and continuous spread of the disease.
- Adverse events in response to anti-TB drugs.
- Some drugs for drug-resistant TB are not available everywhere and are less effective, more toxic, and require longer use.
- Co-infection of TB and HIV, where their combined treatment involves a high pill count with associated adherence problems, overlapping toxicity profiles, drug interactions and risk of immune reconstitution syndrome.
- Prophylactic therapy of latent TB (TB infection without symptoms) is also associated with problems.

Aiming shortening of treatment, some efforts have been made, including application of alternative drugs. Unfortunately they resulted in severe adverse effects.
In an attempt to optimize the response, the World Health Organization (WHO) developed the Directly Observed Therapy Short course (DOTS), but due to its expensiveness and labor intensity it became a burden on public health programs, especially in the developing countries with limited resources [8].

From the above, may be summarized that part of the problem with returned TB and one of the reasons for the appearance of MDR- and XDR-TB, as well as the HIV TB co-infection is the ineffectiveness of the today available TB therapy, consistent of the below listed classical anti-tubercular agents.

CLASSICAL ANTI-TUBERCULAR AGENTS IN USE

The currently applied classical drugs, used to treat tuberculosis, include broad spectrum and narrow spectrum agents and different drug combinations (“cocktails”) targeting different type of tuberculosis [3], traditionally divided into two lines. The “First line” drugs include fundamental chemotherapeutics of choice, like Isoniazid and Streptomycin. They have been highly effective, but very susceptible to resistant strains. The “Second line” tuberculostatics are used mainly in the conclude therapy. Although less effective, in the “cocktail therapy” they contribute to overcoming the resistance.

First Line anti-tuberculosis agents:

Streptomycin

Streptomycin was discovered in 1944, by Waksman (Nobel Prize winner 1952) and Schats, and was the first really effective drug against tuberculosis. It is an aminoglycoside antibiotic isolated from Streptomyces griseus with minimal inhibitory concentration (MIC) value of 1 μg ml<sup>-1</sup>. Due to many toxic manifestations on peripheral, central nervous system and hypersensitivity reactions it is not a drug of popular choice, although included in the “cocktail therapy” [10]. Through the years different derivatives and analogs of Streptomycin have been synthesized and evaluated. After the Kanamycins and Gentamycins, the extremely successful generation of Tobramycin, Dibecacin, Sisomycin, Netilmicin, Pentisomycin was born. The lack of the vulnerable 3′-OH in their structure was helpful with overcoming the bacterial resistance due to 3′-O-Phosphotransferase and profiled them (together with Amikacin) as active against extremely pathogenic strains such as Pseudomonas Aeruginosa and Enterobacteriaceae, but the effect upon M. Tuberculosis remained insufficient.

In the crucial search for new and more effective anti-tuberculosis agents, almost all commonly known and applicable antibiotics have been tested for activity against M. tuberculosis and other mycobacteria, some found to be significantly active [11], such as the macrolides Erythromycin, Roxithromycin, Clarithromycin and Capreomycin [10, 12-14].

After the discovery of Rifamycins by P. Sensi and coworkers (1959) (Fig. 1) [10], Rifampicin produced a small revolution in the anti-TB therapy becoming an antibiotic of first choice (especially in combinations with Isoniazid and Ethambutol) and a prototype

![Rifampicin and Rifapentine structures](image)

**Fig. 1. Structure of some Rifamycins.**
generated a number of effective new analogs. Synergic effect with Trimethoprim was manifested.

**Isoniazid**

![Isoniazid structure](image)

**Fig. 2. Structure of Isoniazid.**

Discovered by Domagk in 1952 (a Nobel Prize winner for the first sulfonamide) it becomes one of the most active and successful agents to treat tuberculosis. Isoniazid (Fig.2) is a prodrug that requires activation. It is orally active and exhibits bacteriostatic action on the resting bacilli and is highly active against the *M. tuberculosis* complex (*M. tuberculosis*, *M. bovis*, *M. atricanum* and *M. Microti*) with very low MICs (0.02-0.06 µg ml⁻¹) against these pathogens. Isoniazid inhibits the mycolic acid biosynthesis in *Mycobacterium tuberculosis* by affecting an enzyme mycolate synthetase, unique for mycobacteria [10].

**Hydrazones of Isoniazid as Tuberculostatics**

The impressive Isoniazid was put as a starting point in the search for new active derivatives and analogs, yielding a generation of hydrazones as active anti-TB drugs (Fig. 3) [15-20].

**Ethambutol**

![Ethambutol structure](image)

**Fig. 4. Structure of Ethambutol.**

Ethambutol (Fig. 4) synthesized by Wilkinson in 1961 is a synthetic amino alcohol, orally effective bacterio-static agent and active against most strains of *Mycobacterium*. The proposed site of action of this first line drug ranged from trehalose dimycolate, mycolate and glucose metabolism to spermidine biosynthesis [10].

![Hydrazones of Isoniazid](image)

**Fig. 3. Structure of some Hydrazones of Isoniazid.**
Pyrazinamide

Pyrazinamide (Fig. 5) is a structural analog of nicotinamide. It is also active against semidorminant bacilli not affected by any other drug and has strong synergy with Isoniazid and Rifampicin and shortens the therapy period to 6 months. The drug has no significant bactericidal effect and is thought to act by sterilizing effect [10].

Second Line anti-tuberculosis agents:
p-Aminosalicylic acid (PAS)

The antimycobacterial activity of the already known PAS (inactive against other bacteria) (Fig.6) was reported in 1946. Following the developed Directly Observed Therapy Short course (DOTS) it is rarely used today, but occasionally in the regimen for the treatment of tuberculosis caused by MDR-TB [10]. The hydrazide of PAS (Apacizin) exhibited good tuberculostatic activity [21].

Ethionamide and Protonamide

Two homologues compounds have been proposed as second line tuberculostatics. The different mechanism of action expressed by Ethionamide (Fig.7) and Protonamide (Fig.7), makes them an interesting objects for further application. The mode of action of the activated form of Ethionamide is established [22, 23]. Due to the distinct activation mechanisms from Isoniazid, clinically derived M. tuberculosis ethionamide mutants, are not cross-resistant with Isoniazid. Ethionamide has activity against M. tuberculosis, M. bovis and M. smegmatis. It is also activ against M. leprae [10, 24].

There is complete cross resistance between Protonamide and Ethionamide, and resistance emerges rapidly. Protonamide has activity against mycobacterial species including M. leprae and M. avium. Protonamide killed M. leprae more quickly than Ethionamide [10].

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Cycloserine

D-Cycloserine (Fig. 8), is a structural analogue of amino acid D-alanine, possesses activity against a wide range of bacteria, and inhibits M. tuberculosis at concentrations of 5-20 μg ml⁻¹. Cycloserine results in the central nervous system toxicity and can also generate psychotic states with suicidal tendencies and epileptic convulsion.

Other drugs in use in the current anti-tuberculosis therapy:

Fluoroquinolones

These are synthetic derivatives of nalidixic acid (Fig. 9) and display broad-spectrum antimycobacterial activity, as Ciprofloxacin and Ofloxacin used as a part of multi drug regimens in clinical treatment of patients infected with M. tuberculosis and M. avium.

Structural modification of Fluoroquinolones to optimize antimycobacterial activity have been extensively performed to generate more effective candidates [26, 27].

Some anti-TB drugs comprising variety of heterocyclic systems are shown in Fig.10:

The bactericidal Clofazimine is effective against M. tuberculosis-infected macrophages. A possible synergy with Isoniazid has been reported. The mode of action is not defined.
**Linezolid** opened a new class of oxazolidinone antibiotics. No Linezolid cross-resistance has been observed with sensitive *M. tuberculosis* or pan-resistant *M. tuberculosis* strains. It is bacteriostatic against enterococci and staphylococci, and bactericidal for strains of streptococci.

**Thioridazine** is active against TB and has been used to probe the mechanism of action of the phenothiazines as TB agents. It is also active against two strains of malaria [10].

The above listed anti-tuberculosis drugs have been widely used, in the recent past as main agents in anti-tubercular therapy. Unfortunately the prolonged therapy course leads to rapid emergence of resistance and makes them ineffective. The helplessness in the fight with the overgrowing resistance started the rapid and intensive search for new anti-tubercular agents and simultaneous improvement of all known medicinal approaches to fight the returned tuberculosis.

**SUMMARIZED SIGNIFICANCE AND EFFECTIVENESS OF THE CLASSICAL ANTI-TB DRUGS**

Most of the above listed anti-tuberculosis drugs are still in use (often in “cocktails”) in the urgent need to treat the returned TB. Unfortunately the prolonged implementation of the classical drugs developed a growing resistance and the drugs “of yesterday” became gradually less effective and incapable to meet the new challenges, especially those of MDR-TB, XDR-TB, and HIV-TB co-infections. The helplessness in the severe TB cases triggered a broad and intensive search for new and improved anti-TB agents to complete on the other side the development of supplementary medicinal approaches to fight the returned tuberculosis.

**ANTITUBERCULAR AGENTS UNDER DEVELOPMENT**

**CHALLENGES IN NEW ANTI-TB DRUGS DEVELOPMENT**

A major challenge in TB drug development is the difficulty to identify new chemical entities active against *M. tuberculosis*. The deciphering of the mycobacterial genome in 1998 aroused the hope of disclosing a clear and common mechanism of action of anti-TB agents, reliable to be used at the design and optimization of new active molecules. Unfortunately the direct utilization of such a valuable information happened to be limited by the contradictory data for the numerous targets crucial for the tuberculosis bacilli, such as: enzymes participating in the biosynthesis of lipoarabinomannan and phthiocerol dimycoserosate - major cell wall-associated components, enzymes participating in the biosynthesis of the mycolic acid-arabinogalactan-peptidoglycan complex, genes involved in regulatory networks and the enduring hypoxic response, etc. [28-32]. The problem triggered a global offensive resulted in a massive and somewhat random search for
active molecules, especially in the field of heterocyclic chemistry. Several promising new drug candidates have already reached the phase of clinical testing [8].

**New drug candidates with novel mechanisms of action**

A number of new anti-TB drugs are in the late stages of development following novel mechanisms of action, that overcome the cross resistance with First line drugs, exhibit excellent activity against *M. tuberculosis* and reduce the duration of treatment and dosing [33].

**Diarylquinoline TMC207 (Johnson & Johnson)**

Diarylquinoline TMC207 (Fig. 11) is an extremely promising member of a new class of anti-mycobacterial agents. Its spectrum is unique in its specificity to mycobacteria. Pharmacokinetic and pharmacodynamic studies in mice showed long plasma half-life, high tissue penetration and long tissue half-life [10, 34]. Diarylquinoline TMC207 is currently in phase IIa clinical trials [35].

**Nitroimidazofurans and Nitroimidazopyrans**

Nitroimidazofurans (Fig. 12) originally used as radio sensitizer in cancer chemotherapy have been reported to possess in vivo antitubercular activities.

However, because of mutagenic side effects this series of compounds could not enter into clinics for the treatment of tuberculosis. One of the compounds PA – 824 has expressed activity both in the replicating and latent *M. tuberculosis* cells with MIC from 0.015 to 0.25 µg ml⁻¹. Another orally active analog - PA 1343 has been developed and is in preclinical studies with MIC of 0.015 µg ml⁻¹ [36]. Comparable susceptibility of MDR strains of *M. tuberculosis* and PA-824 indicates that there is no cross resistance with current drugs [3, 37].

**PA-824 and its biphenyl analogs**

![Fig. 13. Structure of PA-824 and its biphenyl analogs.](image)

A series of analogs (Fig. 13) of the new tuberculosis drug PA-824 have been prepared. Para-linked biphenyl analogues are the most active, followed by the meta- and ortho-linked ones [38].

**OPC-67683**

OPC-67683 (Fig.14) is closely related to PA-824 and may share a similar mode of action. It is active against strains resistant to Rifampin, Ethambutol, Pyrazinamide, Isoniazid and Streptomycin. The exhibited *in vitro* potency against *M. tuberculosis* H37Rv shows MIC of 0.012 µg ml⁻¹. It is active against *M. kansasii* and *M.*
tuberculosis while PA-824 showed activity only against *M. tuberculosis*. Phase I and Phase II studies have been conducted but results are not available yet [10, 35].

**Isoxyl (Thiocarlide)**

Thioacetazone

![Thioacetazone](image)

Isoxyl

![Isoxyl](image)

Fig. 15. Structure of Thioacetazone and Isoxyl.

Among the diacyl thioureas Isoxyl was found to be clinically more useful than the more toxic Thioacetazone. It inhibits mycolic acid biosynthesis in *M. bovis* during 6 h exposure [39, 40].

**Thiolactomycin**

![Thiolactomycin](image)

Thiolactomycin (Fig.16) belongs to a small group of thioetheric acid antibacterials and is an unique thiolactone exhibiting anti-TB activity with MIC of 5 µg ml\(^{-1}\) [41].

**Tryptanthrin**

Tryptanthrin (Fig. 17) is a potent structurally novel indolo-quinazolinone alkaloid, active against MDR-TB with a MIC of 0.5-1.0 µg ml\(^{-1}\). But *in vivo* data and *in vitro* toxicity are needed before this structural prototype is applied in MDR-TB [42, 43].

**Clofazimine Analogs**

Few of tetramethyl piperidine substituted phenazines have significantly higher *in vivo* activity against *M. tuberculosis*, including MDR clinical strains than clofazimines (Fig. 18) [44, 45].

**Oxazolidinones**

Oxazolidinones (Fig. 19) are synthetic, orally active antibacterials discovered by DuPont.

Thiomorpholine analogues of U-100480 with the biphenyl methyl group replacing the acetamido methyl oxazolidinone moiety showed potent *in vitro* activity against *M. tuberculosis*.

Unfortunately none of the compounds of this series is in advanced stage of clinical trial [46].

**Diterpenoids**

These compounds (Fig. 20) known for various medicinal values have recently been screened for antituberculosis activities against *M. tuberculosis*. Many analogs have shown potent antimycobacterial activity and it has been established that benzoaxazole moiety is not essential for the activity.

All of the tested compounds were isolated from natural sources [47].

**Purines**

9-Benzyl purines (Fig. 21) with a variety of substituents in the 2-, 6- and/or 8- position have been found to possess high inhibitory activities against *M. tuberculosis* with IC\(_{50}\) ≤ 1.5 µg ml\(^{-1}\) [48].

**Thiazidine thiones**

Thiazidine thiones (Fig. 22) derivatives of dithiocarbamic acids have been screened against *M. tu-
**Clofazimine analogs**

![Clofazimine analogs](image)

Fig. 18. Structure of Clofazimine analogs.

**B 4157**

**B 4154**

**DUP-721**

**U-100480**

**PNU-100480**

**U-101603**

**U-101244**

Fig. 19. Structure of Oxazolidinones.

**Berculosis.** One of the compounds have shown potent in vitro antitubercular activity against *M. tuberculosis* H37Rv even in resistant strains and also protected the mice marginally in experimental tuberculosis [3].

**Simple Carbohydrate derivatives**

Based on the observation that simple sugar derivatives (Fig. 23) possess inhibitory activity against the enzymes involved in cell wall biosynthesis, many simple monosachcharide derivatives have been tested against *M. tuberculosis* H37Rv and have shown potential activity in vitro. Few of the compounds have shown potent activity in vitro even in many clinical MDR of *M. tuberculosis* strains. However, many compounds displayed toxicity in the animals and an effort in this direction is continued [3].

**Benzopyran-2-ones**

Antitubercular activity in this class of molecules was reported while investigating the anti HIV activity in natural products (+) Calanolide and (-) Calanolide A (Fig.24), where these compounds demonstrated
antimycobacterial activity against *M. tuberculosis* H37Rv to the extent of 96 and 98 % with MIC values as low as 3.13 μg ml⁻¹ [3].

*Dipiperidine SQ-109 (Sequella Inc.)*

SQ109 (Fig. 25) inhibits mycobacterial cell wall synthesis. SQ109 is a potential anti-TB drug that has
entered phase I/II clinical trials. It has low MICs against both susceptible and resistant MTB strains. Clinical trials are ongoing to establish its future role in TB treatment [8, 10].

**Pyrrrole derivatives as anti-tubercular agents**

In the variety of heterocyclic compounds explored in the search for reliable starting platforms for new anti-TB drugs development, pyrrrole derivatives gained a special research attention in the last decades. Besides the life important role of pyrrrole in the natural products chlorophyll, Vitamin B12, bilirubin [51], its structural presence was associated with extremely diverse biological effects, such as CNS depressive [52], antitumor [53], antihypertensive [54], antioxidant [55], anticonvulsive [56], HIV-inhibiting [57], etc. Recently the placement of pyrrrole cycle at the design of new tuberculostatics successfully yielded a series of promising products found to be active against standard and drug-sensitive *M. tuberculosis* strains in vitro [58-60].

**Pyrrrole LL- 3858 (Sudoterb) (Lupin Limited, India)**

On the basis of suggestions derived either from a pharmacophoric model or from a structure-activity relationship, analysis of many pyroles previously described [63-65] led to the design and synthesis of new analogues of 1,5-(4-chlorophenyl)-2-methyl-3-(4-methylpiperazin-1-yl)methyl-1H-pyrrrole (BM212) (Fig. 27). Although some non tuberculosis mycobacterial strains were found to be sensitive, MIC values were higher than those toward *M. tuberculosis*. The most active compound possessed a MIC of 0.4 μg ml⁻¹ [66, 67].

After the development of anti-tuberculosis agents BM 212, Sudoterb and a number of perspective active analogs, the derivatives of pyrrrole focused additional research interest. On the other hand due to the diverse biological activities of the hydrazones, they constitute an important class of compounds for new drug development. The popular anti-tubercular activity of Isoniazid and its derivatives triggered the development of new hydrazones as one of the approaches in the urgent search for new tuberculostatics.

**Exploring pyrrrole hydrazones (some own investigation in brief)**

The idea to combine the active principles of pyrrrole and hydrazone moieties mentioned above motivated us to synthesize in our Laboratory of Organic synthesis at University of Chemical Technology and Metallurgy (UCTM) more than 200 new hydrazones containing pyrrrole cycle, presented with the general formula given on Fig. 28. In vitro evaluations of the new compounds as potential antitubercular agents performed at National Institute of Allergy and Infectious Disease (NIAID) with TAACF acting as a Contractor registered some active hits exhibiting up to 100 % inhibition of *Mycobacterium tuberculosis* H37Rv at 6.25 μg ml⁻¹, IC50/IC90 ≤ 0.2 μg ml⁻¹ and MIC <0.1 μg ml⁻¹.
where X is a halogen atom (Cl, F, Br); n is the number of methylene groups (n=1,2 or 3) and \( R^* \) is a residue of a carbonyl reagent \( R^* = O \), whereat more than 20 aromatic or heteroaromatic aldehydes/ketones have been used. Some structure/property relationships and simplified QSAR models were derived. The registered most active hits may serve as reliable prototypes in further ligand based design and optimization of novel and more potent antitubercular agents [68-74].

**OTHER CONTEMPORARY AREAS OF DEVELOPMENT OF ANTI-TB AGENTS**

**Marine natural products**

*Kahalalides A* (Fig. 29), isolated from the Sacoglossan mollusk Elysia rufescens, inhibited the growth of *M. tuberculosis* H37Rv. Similarly, *Litosterol* and *Nephalsterol C*, the C19 hydroxy steroids, isolated from a red sea Neptheasps; had 90 and 96 % inhibitory activity against *M. tuberculosis* H37Rv. Heteronemin a Sesqeterpene isolated from a red sea sponge; displayed antitubercular activity against *M. tuberculosis* H37Rv with MIC 6.25 μg ml⁻¹ and IC50 1.3 μg ml⁻¹ [3].

**ATP Synthase Inhibitor FAS20013 (FASgene)**

FAS20013 is a novel compound identified by Fasgen and belongs to the class of β-sulphonylcarboxamides. It is very effective in killing MDR-TB organisms that are resistant to multiple drugs currently in use. The agent is up to 100% bioavailable when administered orally and is thought to act through inhibition of ATP synthase. However, available scientific publications assessing its efficacy are of poor quality [75].

**Translocase I Inhibitor (Sequella Inc.)**

Sequella is developing a series of translocase inhibitors for the potential treatment of tuberculosis. The compounds specifically inhibit mycobacterial translocase I, an enzyme required for bacterial cell wall synthesis. Preclinical evaluation of the compounds is planned [76].

**InhA Inhibitors (GlaxoSmithKline-TB Alliance)**

InhA, the enol reductase enzyme from *Mycobacterium tuberculosis*, catalyses the last step in the fatty acid biosynthesis pathway (FAS II). Frontline anti-tuberculosis drugs such as Isoniazid target this enzyme.
Consequently, InhA inhibitors that do not require activation are attractive candidates for drug discovery. A possible limitation for this kind of compounds is that cross-resistance with Isoniazid may easily occur [77].

**Isocitrate Lyase Inhibitors**  
*GlaxoSmithKline-TB Alliance*  
The isocitrate lyase enzyme has been shown to be essential for long-term persistence of *M. tuberculosis* in mice, but not required for bacilli viability in normal culture or hypoxic conditions. The absence of this enzyme orthologs in mammals should facilitate the development of glyoxylate cycle inhibitors as new drugs for the treatment for tuberculosis. The structure of isocitrate lyase enzyme’s active site is making the screening for inhibitors particularly lengthy and laborious. The active site of this enzyme, indeed, appears not to be easily and effectively reached by compounds [78].

**Pleuromutilins**  
*GlaxoSmithKline-TB Alliance Partnership*  
The Pleuromutilins represent a novel class of antibiotics derived from a natural product and inhibiting the growth of *M. tuberculosis in vitro* [35]. Recent studies have shown that cross-resistance might occur among Pleuromutilins and Oxazolidinones.

**Nanoparticles and drug delivery systems**  
Pandey and colleagues demonstrated that the nanoparticles provided sustained release of the anti-TB drugs and considerably enhanced their efficacy after oral administration. Treatment of *M. tuberculosis* - infected mice with the nanoparticle-bound drugs resulted in complete bacterial clearance from the organs. Free drugs were able to produce bacterial clearance only after daily administration of 46 doses. Although identifying novel anti-TB agents remains a priority, the development of the nanoparticle-based delivery systems for currently used agents may represent a cost-effective and promising alternative [79].

**GLOBAL COORDINATION OF ANTI-TB DRUGS DEVELOPMENT AND RESEARCH**  
The TB drug market is associated with insufficient profit opportunity or investment return to instigate pharmaceutical industries to develop new drugs. The cost of developing a new drug is estimated at $115 to $240 million. To be profitable, market prices of new drugs should be relatively high, whereas the cost of the standard regimen is only about $11 per patient. In response to the reluctance of pharmaceutical industries, governments and nongovernmental organizations have started to invest in TB drug research and development. In the 1990s, the *United States Centers for Disease Control and Prevention* (CDC) established the *Tuberculosis Trials Consortium* (TBTC) [8]. In 2000, private and public sector partnerships formed the *Global Alliance for TB Drug Development* (GATB) [80], a non-profit venture that supports the discovery and development of cost-effective new drugs. Various other research consortia are testing new drugs in preclinical and clinical trials. Large funding agencies, such as the *European & Developing Countries Clinical Trials Partnership* (EDCTP) and the *Bill & Melinda Gates foundation* are supporting these initiatives [8]. Other potential users such as *Stop TB Partnership* [81] are closely engaged with the fight against TB and search collaboration in further development of new anti-tuberculosis agents.

One of the most active organizations is the *National Institute of Allergy and Infection Diseases* (NIAID), which has clearly stated its interest and support in the development of new potential tuberculostatics. The NIAID tuberculosis screening programs have contributed to the design and implementation of several new assays useful in evaluating new compounds for antitubercular activity, including several enzymes assays [82, 83]. Thus, the development of an efficient high throughput screening (HTS) approach was initiated, in order to provide to the TB research community growth inhibition data on large compound libraries that could be publically released [7].

**USAID’s Commitment**  
The United States Agency for International Development (USAID) aims to support the implementation of the STOP TB Strategy and contribute significantly to the global reduction of morbidity and mortality associated with tuberculosis. In this relation the USAID’s specific goals are:

- By 2015, to halve TB prevalence and deaths in USAID priority countries; and
- By 2011, to detect at least 70 % of estimated cases and successfully treat at least 85 % of those cases in USAID priority countries.
USAID contributes to the achievement of STOP TB global targets for treatment success and case detection by focusing on country level support to implement the STOP TB Strategy in priority countries (Table 1) [84].

These priority countries (or sub-regions of these countries) were selected based on the following criteria: high burden of TB cases; high incidence of TB (case notification rates over 100/100,000); high HIV/AIDS prevalence (TB/HIV co-infection); prevalence and/or potential for drug resistance; and lagging case detection and treatment success rates.

In addition to the countries noted above, USAID supports the Europe and Eurasia Regional Bureau, Latin America and the Caribbean Regional Bureau, Africa Regional Bureau, and Regional Development Mission to implement regional and sub-regional activities [84].

Partnerships are a cornerstone of global’s expanded response to TB. The followed approach is to coordinate efforts and investments, provide technical input, strategically support key activities and areas of mutual interests, and ensure that the strategic concerns are addressed. Through Stop TB Regional Partnerships, grants to regional institutions, and regional initiatives, USAID supports regional technical advisors and trainings, information dissemination and networking activities, operations research, and pilot activities [84].

CONCLUSIONS

On the background of the great concern inspired by the apocalyptic picture presenting the current status of the front against TB, a global mobilization has been triggered on. The typical for the last decades growing pessimism provoked by the fact that after introduction of Rifampin no decisive success has been detected in the search for the missing powerful anti-TB drug has to step back. There are serious indications for a hopeful “light in the dark tunnel”:

- Reliable leaders of new generation of tuberculosis is in advanced phase of development
- Soon new anti-TB drugs will be welcomed in already new environment of additional significant achievements in alternative medicinal aspects of the fight against TB (such as improvements in diagnostics, hygiene, vaccines, clinical treatment etc., out of the scope of the review)
- A global network coordinates and supervises the profound anti-TB research and contributes to its adequate financial provision.

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