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OVERVIEW OF NEW ANTI TB DRUGS

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ABSTRACT

The emergence of multi-drug-resistant strains of M. tuberculosis makes it necessary for the discovery of new drugs, and also implement other modalities of treatment. Eperezolid and linezolid are oxalidinones which are in phase II clinical trials. Other oxalidinones like AZD5847 and PNU100480 are being evaluated in a phase I trials. Regimens based on a higher dose of rifampin in humans are also being evaluated. Rifapentine (10 mg/kg) was approved for the treatment of pulmonary TB in 1998. Fluroquinolones like Ofloxacin, Ciprofloxacin, Lomifloxacin, levofloxacin, sparfloxacin and Moxifloxacin are effective against M. tuberculosis and are in various phase of development. Newer molecules like TMC207, nitroimidazoles like PA-824 and OPC-67683 are in phase II. Diamines like SQ109 has shown to have in vitro action between SQ109 and isoniazid and especially rifampin. SQ609, a dipiperidine, which is an inhibitor of translocase, involved in cell wall synthesis, is in preclinical studies. Sudoterb (LL3858) is found to have bactericidal activity against both drug senstitive and MDR-TB. BTZ-043 (NM4TB Consortium), FAS20013, LL3858, CPZEN-45, are also in various stages of development. New potential drug molecules and drug targets are also being evaluated. New techniques like using FRIGATE, and Nanocarriers, chemical investigations on the whole plants Gentiana, methanolic root bark extract of Leucophyllum, Cinnamic derivatives are being evaluated for their role in anti TB activity. Immunomodulation with 1, 25-dihydoxyvitamin D and resection of cavitary or badly damaged lung tissue could be used as a adjuvant therapy in tuberculosis. Enumerous vaccines are in various stages of preclinical development.

INTRODUCTION: Tuberculosis (TB) is more prevalent in the world today than at any other time in human history. Mycobacterium tuberculosis, the pathogen responsible for TB, uses diverse strategies to survive in a variety of host lesions and to evade immune surveillance. The emergence of multi-drug-resistant strains of M. tuberculosis makes the discovery of new molecular scaffolds a priority, and the current situation even necessitates the re-engineering and repositioning of some old drug families to achieve effective control.

This article will deal with newer drugs which are already in use, ones which are in various phases of development, identifying potential targets, the development of new vaccines and immunotherapy,

Current chemotherapy for tuberculosis dates back to the 1950s and is arduous, lengthy, and remains extremely difficult to complete in many of the highest burdened areas. The pipeline of potential new treatments has been fulfilled with several compounds in clinical trials or preclinical development with

promising activities against sensitive and resistant Mycobacterium tuberculosis strains. Compounds as gatifloxacin, moxifloxacin, metronidazole or linezolid already used against other bacterial infections are currently evaluated in clinical phases 2 or 3 for treating tuberculosis. In addition, analogues of known TB drugs (PA-824, OPC-67683, PNU-100480, AZD5847, SQ109) and new chemical entities (TMC207,) are under development.

Already in use:

1. Oxalidinones: Eperezolid and linezolid have a wide activity against a wide variety of organisms, including mycobacteria. The mode of action is by inhibiting protein synthesis by binding to 70S initiation complex. Linezolid -containing chemotherapy for the treatment of XDR-TB significantly improves clinical symptoms, promotes lesion absorption and cavity closure, and accelerate sputum conversion in a number of clinical trials [1].

   Its use in TB has been limited primarily by safety issues, particularly myelosuppression and peripheral or optic neuropathy typically associated with administration for 2 weeks or longer, but it has been used off-label to treat MDR-TB and XDR-TB patients [2, 3]. Other authors have suggested comparable efficacy and decreased toxicity can be achieved by halving the dose of linezolid in MDR-TB treatment to 300mg daily, but only limited clinical data are available to date with this regimen [4, 5]. Currently phase II trials are on [6].

   Pfizer is developing PNU100480 and AstraZeneca is developing a compound known as AZD5847. PNU10048 has demonstrated greater efficacy than linezolid *in vitro* studies [7]. Phase I clinical trials have been under taken [8]. AZD5847 and PNU100480 are being evaluated in a phase I study [9].

2. Rifamycins are particularly effective against mycobacteria, and are therefore used to treat tuberculosis, leprosy and mycobacterium avium complex (MAC) infections. The rifamycin group: Rifamycin A, B, C, D, etc. (the "classic" rifamycin drug, Rifampicin, Rifabutin, Rifamide a derivative of Rifamycin B is used against gram-positive cocci causing respiratory tract infections and against gram-negative and gram-positive organisms in biliary tract infections. Rifampin high dose: Its standard dose in TB treatment is 10 mg/kg of body weight, corresponding to 600 mg in most populations. Results from an efficacy study in mice predicted a one-third reduction in TB treatment duration when the rifampin dose was increased by 50% [10].

   Very limited data is available on the efficacy of regimens based on a higher dose of rifampin in humans. A short regimen of a high dose of rifampin (1,200 mg daily or every other day) with a high dose of isoniazid (900 mg) and streptomycin (1,000 mg) daily yielded almost 100% sputum culture conversion after 3 months [11].

3. Rifapentine: Rifapentine (10 mg/kg) was approved for the treatment of pulmonary TB in 1998. It allows for intermittent dosing at wider intervals, which facilitates observed treatment [12]. However, regimens with rifapentine and isoniazid once weekly in the continuation phase of treatment are slightly inferior to regimens with rifampin and isoniazid twice weekly, especially in patients with cavitary TB. [13] A high rate of mycobacterial monoresistance to rifamycins was seen in HIV-infected patients treated with rifapentine and isoniazid [14]. The use of rifapentine once weekly has therefore been restricted to HIV-negative pulmonary TB patients without cavitation and with a negative sputum culture after the intensive phase of treatment [15].

4. Fluoroquinolones (FRQs): The fluoroquinolones are registered as second-line anti-TB drugs. Fluoroquinolones have bactericidal activity against M. tuberculosis. FRQs inhibit the DNA gyrase, an enzyme involved in DNA replication. [16] There is no cross resistance between these agents and other antituberculosis drugs. Ofloxacin, Ciprofloxacin, Lomifloxacin, levofloxacin, sparfloxacin and Moxifloxacin are effective against M. tuberculosis. [17] In particular, they are distributed broadly throughout the body, including within cells, which explain their efficacy against intracellular mycobacterial [18, 19].

5. Gatifloxacin and Moxifloxacin is undergoing evaluation in a phase III trial, testing its ability when substituted in the first-line regimen for either ethambutol (gatifloxacin, moxifloxacin) or isoniazid (moxifloxacin) to shorten treatment of DS-TB from the standard 6–9months [20].

Newer Molecules:

1. Diarylquinolines: The most active diarylquinoline (TMC207, also called R 207910, or compound J) is clinical trials, discovered by Janssen and being developed in parallel for MDR-TB (by Tibotec [21]. TMC207 inhibits the mycobacterial ATP synthase enzyme a novel mechanism, exhibits synergy with Pyrizinamide *in vitro* [22, 23]. It is active against susceptible and MDR strains. It has a narrow-spectrum. TMC 207 is in early phase II trials. Earlier trials with TMC 207 have demonstrated good sputum conversion and safety profile [24].

2. Two nitroimidazoles, PA-824 and OPC-67683, are currently in clinical trials for the treatment of TB and the outcome of these may determine the future directions of drug development for anti-tubercular nitroimidazoles.

   PA-824 is a prodrug that needs the mycobacterial glucose-6-phosphate dehydrogenase (FDG1) or its cofactor, coenzyme F420, to be transformed into an active form. Activated PA-824 inhibits the synthesis of proteins and cell wall lipids. PA-824 activity is limited to *M. tuberculosis* complex. PA-824 is active in susceptible and resistant *M. tuberculosis* strains.

   No cross-resistance with standard anti-TB drugs has been observed. [25] It is being developed for TB by Otsuka Pharmaceutical. It has demonstrated good activity *in vitro* and *in vivo* mouse models. Phase II trials on going [26]. It could be useful in treatment of MDR and XDR TB. Its optimal formulation and its role in TB treatment in humans still need to be established.

   OPC-67683 is a nitro dihydroimodazooxazole active against Tuberculosis. It acts by inhibiting mycolic wall synthesis. It is bactericidal and good activity in vitro and in experimental animals. It in undergoing phase II, trials to evaluate the proportion of MDRTB patients receiving either 100 or 200mg twice daily of orally administered OPC-67683 in addition to a standardized second-line TB regimen who achieve sputum culture conversion to negative within 2 months, as well as pharmacokinetics and safety [27].

3. Diamines. A library of more than 60,000 compounds was generated by synthesizing ethambutol analogues with 1,2-diamine pharmacophore. So far, the most promising diamine candidate from this library for TB treatment is SQ109 [28].

   a. SQ109. SQ109 related to ethambutol inhibits mycobacterial cell wall synthesis; the exact target is not yet known. No cross resistance is seen between the other drugs for tuberculosis Synergistic activity was shown in vitro between SQ109 and isoniazid and especially rifampin. Synergy was even present in rifampin-resistant strains. Streptomycin had an additive effect on SQ109 activity; ethambutol and pyrazinamide had no effect on the activity of SQ109 [29]. SQ109 has been reported to have synergistic activity with isoniazid and rifampicin in vitro and in animal models. It has been evaluated in phase I studies. Phase II trials are on going [31].

   b. SQ609, a dipiperidine (from Sequella but got from Sankyo, Japan), which is an inhibitor of translocase, involved in cell wall synthesis, is in preclinical studies. [32]

4. Sudoterb (LL3858) is a pyrrole derivative that has been evaluated by Lupin Limited. The pyrroles were originally reported by Lupin as having bactericidal activity against both drug sensitive and MDR-TB and also having in vivo efficacy [33, 34].

5. BTZ-043 (NM4TB Consortium): This is from the Benzothiazinone class. It Inhibits decaprenyl-phosporyl-β- D-ribose 2'-epimerase (DprE). This is in Preclinical stages [35].

6. FAS20013, a sulfonyl tridecamide (from FASgen) is also being developed against MDR TB. It interferes with MTB cell wall synthesis and is expected to be effective against dormant bacteria [36].

7. Pyrroles: The mycobacterial target of LL3858 is not yet known. Since LL3858 is active against *M. tuberculosis* strains that are resistant to available anti-TB drugs, the target probably differs from the targets of the currently used drugs. In the search for compounds with activity against mycobacteria and fungi, several pyrrole derivatives have been developed. LL3858 is being investigated in phase I clinical trials. A fixed-dose combination called LL3848, containing LL3858 and the standard, first-line anti-TB drugs, is also being developed [37].

8. CPZEN-45 by Lilly Partnership Semisynthetic, in Preclinical stages [38].

New Potential Drug Molecules:

1. MetAP is a metalloprotease that removes the N-terminal methionine during protein synthesis. N-terminal methionine excision (NME) is a universally conserved process required for the post-translational modification of a significant part of the proteome. 7-bromo-5-chloroquinolin-8-ol (CLBQ14)-a congener of clioquinol (CQ) as a potent and selective inhibitor of two methionine aminopeptidases (MetAP) from M. tuberculosis: MtMetAP1a and MtMetAP1c [39].

2. Vavříková E screened for *in vitro* antimycobacterial activity in new isoniazid hydrazones [40].

3. Phenothiazines particularly thioridazine for the improvement of TB chemotherapy could to be a rational option especially in view of their role as inhibitors of type II NADH dehydrogenase, a key component of respiratory chain of Mycobacterium tuberculosis, thus raising the speculation that they can be effective against latent TB as well [41].

4. Tuberactinomycin resembles Viomycin structurally as well as in its mode of action. It acts by inhibiting protein synthesis. Negative sputum culture at six months ranged from 73% to 80% in the Tuberactinomycin containing regimens compared to 63% in a similar Viomycin containing regimen. Thus Tuberactinomycin was better than Viomycin [42].

5. Twenty new quinoxalines bearing azetidinone and thiazolidinone groups. Quinoxaline derivatives with 2-chloro, dimethylamino and nitro substitutions exhibited in vitro activity, comparable to that of the drug, isoniazid [43].

6. *Mycobacterium tuberculosis* and *Yersinia pestis* (Yp) produce siderophores with scaffolds of nonribosomal peptide-polyketide origin. Compounds with structural similarities to these siderophores are being synthesized and evaluated. [44].

7. Systematically modified functionalized 2-aminochromenes and heteroarene based compounds have shown mycobacterium tuberculosis H37Rv chorismate mutase inhibiting properties *in vitro* [45].

8. New series of Quinoline- oxazolidinone hybrid molecule compounds 8a, 8j and 13a were found to be active at 0.65 µg/mL against Mycobacterium tuberculosis H(37)Rv strain. The mode of action of these active compounds was carried out by docking of receptor enoyl-ACP reductase with newly synthesized candidate ligands 8a, 8j and 13a. [46].

9. Saravanan P *et al*., emphasized the importance of Rv 0183, an exported monoacylglycerol lipase, involved in metabolizing the host cell membrane lipids. Sequence analysis and homology modeling shows Rv0183 is highly conserved throughout mycobacterial species even in Mycobacterium leprae and also significantly divergent from mammalian lipases. Additionally, employing virtual screening using NCI diversity set and ZINC database with criteria of molecules with higher predicted free energy of binding towards Rv0183 than human lipase, potential inhibitors have been identified for Rv0183 [47].

10. Mirandamycin, has broad-spectrum antibacterial activity against *Escherichia coli, Pseudomonas aeruginosa*, *Vibrio cholerae*, methicillin-resistant Staphylococcus aureus, and Mycobacterium tuberculosis. Ymele-Leki P *et al.*, reported the development of a sensitive and robust but low-tech and inexpensive high-throughput metabolic screen for novel antibiotics [48].

11. A novel class of antimycobacterial drug targets has recently been discovered; it is represented by GlgE,

an essential maltosyltransferase that elongates linear α-glucans as part of a synthetic lethal biosynthetic pathway. Inactivation of GlgE causes accumulation of a toxic phosphosugar intermediate, maltose 1-phosphate, which drives the bacilli into a suicidal self-poisoning cycle that elicits a complex stress profile, eventually resulting in DNA damage and death of *M. tuberculosis*. GlgE combines many favorable properties that make it a highly attractive novel drug target for chemotherapy of TB [49].

Novel Drug Targets:

1. The Clp protease complexes provide a means for quality control of cellular proteins; the proteolytic activity of ClpP in concert with the ATPase activity of the ClpX/ClpC subunits results in degradation of misfolded or damaged proteins. Thus, the Clp system plays a major role in basic metabolism, as well as in stress responses and pathogenic mechanisms. M. tuberculosis has two ClpP proteolytic subunits. ClpP1 is essential for viability in this organism in culture. M. tuberculosis has two ClpP proteolytic subunits. In contrast, clpP2 overexpression was toxic, suggesting different roles for the two homologs. Known activators of ClpP protease activity; acyldepsipeptides (ADEPs): drug target [50].

2. Active efflux of drugs mediated by efflux pumps which confer drug resistance is one of the mechanisms developed by bacteria to counter the adverse effects of antibiotics and chemicals. Efflux pumps encoded by Rv0849 and Rv1258c also mediate efflux of these compounds but to lesser extent. Increased kill is observed in *M. tuberculosis* cells by these compounds in the presence of either verapamil. The efflux pump KO mutants were more susceptible to these compounds in the presence of efflux inhibitors. Inhibitors of one or several of these efflux pumps could have a significant impact in the treatment for tuberculosis. Identification and characterization of Rv0849, a new efflux pump belonging to the MFS (major facilitator superfamily) class is reported [51].

3. Targeting DNA gyrase is a clinically validated therapeutic approach using fluoroquinolone antibiotics to target the gyrase subunit A (GyrA) of the heterotetramer. The biological activities of two potent small-molecule inhibitors of GyrB can be characterized to validate its targeting as a therapeutic strategy for treating TB. Aminobenzimidazole inhibitors of GyrB exhibit many of the characteristics required for their consideration as a potential front-line antimycobacterial therapeutic [52].

4. Causative agents of tuberculosis and malaria, synthesize the essential isoprenoid precursor isopentenyl diphosphate via the 2-C-methyl-D-erythritol 4-phosphate (MEP) pathway rather than the classical mevalonate pathway. DXR, the enzyme that carries out the second step in the MEP pathway, has been investigated [53].

5. Fosmidomycin 1a and FR900098 1b, two inhibitors of DXR, do not affect the viability of *M. tuberculosis* cells, due to a lack of uptake. To overcome the absence of the mycobacterial cell wall crossing of these compounds, Ponaire *et al.,* synthesized and tested the inhibition potency of acyloxymethyl phosphonate esters as prodrugs of fosmidomycin 1a, FR900098 1b and their analogs 2a and 2b on Mycobacterium smegmatis. Only the prodrugs 4b-6b inhibited the bacterial growth and could be effective anti-mycobacterial agents [54].

6. Ethionamide (ETA) is a thioamide antibiotic and one of the most widely used drugs as second line agent for the treatment of MDR-TB. Over the years, some studies have emerged to improve the bioavailability of this drug and of its active metabolites. However, inactive metabolites of ETA are still a major drawback in its application against TB. Porous silicon (PSi) materials can be applied to improve the dissolution behavior of poorly water-soluble compounds and to overcome toxicity and other drug-related problems in oral delivery [55].

7. Thymidine monophosphate kinase from Mycobacterium tuberculosis (TMPKmt), which is essential to DNA replication, was selected as a promising target for the design of new inhibitors [56].

8. A new class of 2-(trifluoromethyl)-6-arylimidazo[2, 1-b][1, 3, 4]thiadiazole derivatives has been synthesized by both conventional as well as

microwave assisted method and evaluated for their in vitro antitubercular activity against M. tuberculosis H(37)Rv. Moreover, various drug-likeness properties of new compounds were predicted. Seven compounds from the series exhibited good activity with MIC in range 3.12-1.56µg/ml. The present study suggests that compounds 6b, 6c, 6d, 6e and 6f may serve as promising lead scaffolds for further generation of new anti-TB agents. [57].

9. A series of isoxazole-based compounds, bearing a carboxy moiety at the C3 position, are highly potent and versatile anti-TB agents. Several members of this compound class exhibit submicromolar in vitro activity against replicating Mtb (R-TB) and thus comparable activity to the current first-line anti-TB drugs. Remarkably, certain compounds also show low micromolar activity in a model for nonreplicating Mtb (NRP-TB) phenotype, which is considered a key to shortening the current long treatment protocol [58].

10. The *in vitro* activity of conjugated (6a-f, 7a-d, 9a-c and 11a-c) molecules of arylsulfonamido conjugated oxazolidinones. against Mycobacterium tuberculosis H(37) was tested [59].

New Techniques:

1. New computational docking algorithm FRIGATE which unites continuous local optimization techniques (conjugate gradient method) with an inherently discrete computational approach in force-field computation, results in equal or better scoring accuracies than several benchmark docking programs. By utilizing FRIGATE for a virtual screen of the ZINC library against the Mycobacterium tuberculosis (Mtb) enzyme antigen 85C, Scheich C *et al*., identified novel small molecule inhibitors of multiple drug-resistant Mtb, which bind *in vitro* to the catalytic site of antigen 85C [60].

2. Nanocarriers can cross biological barriers and are able to target cellular reservoirs of Mycobacterium tuberculosis (M. tuberculosis). Nanoparticle-based systems have significant potential for treatment and prevention of tuberculosis (TB). Targeting the drugs to certain physiological sites such as the lymph nodes has emerged as a promising strategy in treating TB with improved drug bioavailability and reduction of the dosing frequency. Nanotechnology based rational targeting may improve therapeutic success by limiting adverse drug effects and requiring less frequent administration regimes, ultimately resulting in more patients compliance and thus attain higher adherence levels. The development of nanoparticle based aerosol vaccine is undergoing which could serve as new platform for immunization [61].

Herbal:

1. Chemical investigation on the whole plants *Gentiana rhodantha* Franch. ex Hemsl. (Gentianaceae) led to the identification of eight new phenolic compounds, rhodanthenones A-D (1-4, resp.), apigenin 7-O-glucopyranosyl-(1→3)-glucopyranosyl-(1→3)-glucopyranoside (5), 1,2-dihydroxy-4-methoxybenzene 1-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (6), 1, 2-dihydroxy-4, 6-dimethoxybenzene 1-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (7), and methyl 2-O-β-D-glucopyranosyl-2,4,6-trihydroxybenzoate (8), together with eleven known compounds, 9-19 [62].

2. Bioactivity-guided fractionation of the methanolic root bark extract of Leucophyllum frutescens led to the identification of leubethanol, a new serrulatane-type diterpene with activity against both multi-drug-resistant and drug-sensitive strains of virulent *Mycobacterium tuberculosis*. Leubethanol was identified by 1D/2D NMR data, as a serrulatane closely related to erogorgiane, and exhibited anti-TB activity with minimum inhibitory concentrations in the range 6.25-12.50 µg/mL [63].

3. Cinnamic derivatives clearly appear as attractive drug candidates to combat TB. So far, literature has reported that they are easy to synthesize and have promising anti-TB activities. Nevertheless, the mode(s) of action of these small molecules remain(s) to date obscure, therefore the implicated molecular mechanisms deserve to be investigated in further detail in the near future. [64]

Immunomodulation: Vitamin D was used to treat TB in the pre-antibiotic era, and its active metabolite, 1, 25-dihydoxyvitamin D, has long been known to enhance

the immune response to mycobacteria in vitro. Vitamin D deficiency is common in patients with active TB, and several clinical trials have evaluated the role of adjunctive vitamin D supplementation in its treatment [65].

Role of Surgery: Recently, few studies on the role of surgery emerged as a light of hope in the management of difficult to treat pulmonary tuberculosis. Pomerantz BJ reported in his patients with severe drug resistance (about 5 drugs) benefited from the resection of cavitary or badly damaged lung tissue when compared with historical control. Certain other studies also conclude that the use of resection lung surgery was associated with overall improved outcome in patients with highly resistant MDR-TB, with a trend toward improvement for those taking fluoroquinolone antibiotics [66, 67].

Newer Vaccines:

1. New generation vaccine, ID93, It is a fusion protein using antigen targets implicated by human T-cell line recognition analysis, in this case Rv1813, Rv3620 and Rv2608 [68, 69].

2. Modified vaccinia Ankara (MVA) 85 vaccine [70].

3. TB vaccine candidates in clinical stages: are (live recombinant Ones: VPM 1002, rBCG30, AERAS-422) Viral Vectored ones are: Oxford MVA85A / AERAS-485, AERAS-402/Crucell Ad35, AdAg85A. Recombinant Protein: M72 + AS01 (GSK M72), Hybrid-I+ IC31 (SSI Hybrid 1 (H1)), Hybrid I+ CAF01 HyVac 4/AERAS 404, +IC31 Recombinant protein (Ag85B plus TB10.4) fusion molecule with adjuvant (IC31). Whole Cell, Inactivated or Disrupted one are *M. vaccae* (Investigational heat killed preparation derived from rough variant of an environmental isolate), Mw [*M. indicus* pranii (MIP)], RUTI [71].

Candidates in Preclinical Studies: are Recombinant Live one are Mtb and MTBVAC. Recombinant Protein ones are HBHA, Hybrid 56 + IC31 [71].

Next Generation Candidates: TB vaccine candidates that are in the research and development stage: Recombinant Live one are HG856, BCG, IKEPLUS M, smegmatis with ESX3 deletion/ complementation, paBCG, Proapoptotic rBCG, rBCG(mbtB)30, rBCG T+BrM. Smegmatis T+B, rBCG TB Malaria, rBCG38, rBCGMex38, Replication deficient rBCG, rM.microti30 rM.microti38, Streptomyces live vector.

Recombinant Protein one are ID93 in GLASE adjuvant, Latency fusion proteins, R32Kda (recombinant 85A).

Viral Vectored ones are Recombi-nant LCMV, pND 14 vector. Others are Ac2SGL Diacylated Sulfoglycolipid, HG856A, HG856SeV, Hsp DNA Vaccine, HVJ Envelope/HSP65 DNA+IL12 DNA, Liporale BCG, Mycobacterial liposomes and proteosomes, NasL3/AM85B conjugate, NasL3/HtkBCG (BCG adjuvant), PS conjugate, pUMVC6/7 DNA, Recombinant B/HPIV, TBioVax, TBVax [71]

Interleukin: Immunity against *M. tuberculosis* is mediated by T-lymphocytes that produce the type 1 (Th1) helper T cell cytokines IFN and interleukin (IL)-2.30 In TB patients, Th1 cytokines predominate at the site of disease, but the systemic immune response in peripheral blood is characterized by enhanced production of the type 2 (Th2) helper T cell cytokine IL-4, and by reduced secretion of IFN and IL-2 by peripheral blood T cells [72, 73].

CONCLUSION: Drastic measures have to be taken to reduce the long and protracted clinical development of new drugs. The emergence of multi-drug-resistant strains of *M. tuberculosis* makes the discovery of new molecular scaffolds a priority, and the current situation even necessitates the re-engineering and repositioning of some old drug families to achieve effective control.

Drugs that are currently in phase 3 development are moxifloxacin and gatifloxacin. In various phases of development, are PA-824 and TMC207, SQ109, AZD5847, and linezolid. Nanotechnology also holds future promise for targeted drug delivery.

Immunotherapy such as new vaccines and vitamin D may serve as adjunctive treatment for prevention and active disease, together with shortening the course of treatment. Bringing newer and more effective antituberculous drugs to market is a global priority and the process must be accelerated.

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