Review Article

Recent Advancement in the Development of Newer Antitubercular Agents: A Review

Habibullah Khalilullah*, Gamal Osman Elhassan, M. U. Khan, Eltayeb E.M. Eid, Riyaz Ahmed Khan, Kamal Ahmed Qureshi
Department of Pharmaceutics and Pharmaceutical Chemistry, Unaizah College of Pharmacy, Qassim University, Al-Qassim, Kingdom of Saudi Arabia

ABSTRACT

Received: 09 Mar 2016
Accepted: 23 Apr 2016

WHO estimates one third of world’s population has latent tuberculosis (TB) which indicates that people have been infected by Mycobacterium tuberculosis but are not yet ill with disease and cannot transmit the disease and 10% of those infected are prone to develop active tubercular infection in their life. In 2011, TB alone remained one of the most important cause of death from infectious disease worldwide. The effective treatments of TB with the frontline drugs requires several months of chemotherapy to eliminate the persistent bacteria. The widespread non compliance in prescribing antitubercular drugs has contributed to the emergence of multidrug-resistant (MDR), and extensively drug resistant (XRD) tuberculosis. Nearly 1.3 million multi/extensively drug resistant TB (M/XRD-TB) cases will need to be treated by 2015. In spite of tremendous advances in technology no new drugs have been introduced since the discovery of rifampin. The drugs such as TMC207, PA-824, OPC-67683, SQ109, Linezolid, and PNU-100480 are still in the phase 2 clinical trials and BDM31343, DNB1, and BTZ043 are the new chemical entities. Bedaquiline (TMC207) is expected to enter phase 3 clinical trials to provide early access to patients with XRD and Pre-XRD-TB, and now Food and Drug Administration (FDA) approved it to treat MDR-TB but the drug has severe heart problem. It is the first drug with a new mechanism of action for TB in more than 40 years and the first and only one specifically indicated for MDR-TB. Efforts are still eagerly awaited to develop novel, fast acting and safer antimycobacterial agents to treat TB in order to win the battle against this millenary scourge. The present review briefly deals with the recent advancement in the development of newer antitubercular agent.

Keywords: Antitubercular agents; Tuberculosis; Tubercular vaccines

1. INTRODUCTION

Tuberculosis (TB) is a dreadful disease caused by Mycobacterium tuberculosis (MTB) and members of the Mycobacterium tuberculosis complex, which includes Mycobacterium tuberculosis itself, Mycobacterium africanum, Mycobacterium bovis,
Mycobacterium caprae, Mycobacterium microti, Mycobacterium pinnipedii and Mycobacterium canetti and is one of the most important health problems worldwide.

TB treatment is challenging, needs accurate diagnosis, screening for drug-resistance and the administration of effective treatment regimens for at least 6 months through directly observed therapy (DOT) and follow-up support. TB can be differentiated as pulmonary (affecting lung) or extra pulmonary (affecting other sites). The drug resistant TB is further divided into multi drug resistant (MDR) TB (resistant to isoniazid and rifampicin) and extensively drug resistant (XDR) TB (resistant either to quinolones or to any one of kanamycin, capreomycin, or amikacin). As per WHO global tuberculosis report 2013, there were an estimated 8.6 million cases of TB and 1.3 million died from the disease, almost one million deaths occurred among people who were HIV-negative and 0.32 million among HIV-positive individuals. Among these deaths, there were an estimated 0.17 million from MDR TB. Compared with 0.45 million incident cases of MDR TB, approximately 1.3 million lives have been saved between 2005 and end of 2011 by implementing collaborative TB/HIV activities and 48% of the HIV positive TB patients were started on antiretroviral treatment (ART). Nearly 10% of infected people developed active TB in their life. Researchers from Stanford University revealed that the MTB can persist in hostile intracellular environment escaping immune cells and drug treatment. They also isolated MTB from bone marrow derived CD271+/CD45-mesenchymal stem cell. Tubercular bacteria are spread all the way through the air by active TB patients and commonly affecting the lungs. The directly observed treatment short-course (DOTS) and a multidrug therapy program developed and executed by World Health Organization (WHO), is one of the most efficient tools against the global plague with great success rate in 2010. The increasing problem of MDR-TB has focused attention on developing new drugs that are not only active against drug resistant TB, but also shorten the lengthy therapy. Unfortunately, the first-line treatment can fail due to deprived compliance and leads to the emergence of MDR-TB. Today we have more number of antitubercular agents in preclinical and clinical development than during the last four decades. In this article we describe not only the chemical entities currently in the clinical trials but also the new vaccines in the developmental pipeline as well as the new diagnostic test either endorsed by WHO or commercialized.

Different criteria for developing new anti-tubercular drugs are reported. A new antitubercular drug should fulfil a number of factors which are as follows:

a) fully validated safety profile;

b) should provide shorter, safer, more effective and cheaper treatment alternatives for MDR-TB;

c) should be able to inhibit new targets so that MDR-TB and XDR-TB can be treated,

d) must be compatible with antiretroviral therapy, as many patients are co-infected with HIV;

and
d) must show no drug interaction with other antitubercular drugs or drug candidates so that a proper regimen comprising at least three active drugs can be constituted.

The past decade has seen an emergence of a promising TB drug discovery (Table 2, 3 and 4). Combining these new drugs with existing TB drugs may provide new regimens that are better tolerated, shorter in duration and with fewer side effects when compared with existing regimens. A number of new therapeutic agents and treatment regimens are under various phases of clinical trials.

After several decades of slow progress in antituberculosis drug development, the pipeline has increased in the past 5 years (figure 1).
Progress is being made through repurposing of old drugs, re-engineering of existing antibacterial compounds, and discovery of new compounds. The most rapid progress has been made by researchers repurposing or redosing known antitubercular drugs such as rifamycins (rifampicin, rifapentine), fluoroquinolones (moxifloxacin, gatifloxacin), and rhiminophenazines (clofazimine). These drugs have entered advanced phase 3 studies. There are several candidates in Phase II and Phase III clinical trials (Table 3 and 4) together with a number of drugs in preclinical development. Many of the chemical entities currently in clinical trials are drugs that were developed to treat other infectious diseases (for example, fluoroquinolone, rifamycins, oxazolidinones and rhiminophenazines) and have since been repurposed. Drug candidates such as bedaquiline, PA-824 and OPC67683 that were initially discovered as antimycobacterial agents and have subsequently been developed as potential TB drugs, approved by the FDA for use as part of combination therapy for adults with MDR pulmonary TB.

Several additional newer compounds are in preclinical development for TB, including the nitroimidazole TBA 354, the fluoroquinolone DC159a, the dipiperidine SQ609, the capuramycin SQ641, the benzothiazinone BTZ043 and the caprazene nucleoside CPZEN45 (Table 2).

2. CURRENT THERAPY FOR TUBERCULOSIS RECOMMENDED BY WHO

WHO has recommended a combination of isoniazid, rifampin, ethambutol and pyrazinamide (DOTS) for a 6 months therapy. Second-line drugs such as aminoglycosides, capreomycin, cycloserin, p-aminosalicylic acid, thioamides and fluoroquinolone has been recommended by WHO for the treatment of MDR-TB. Some of the antitubercular drugs and their mechanism of actions are given in Table 1.

Rifampicin (RIF) is the drug of choice in the TB, which has been modified to rifalazil, rifabutin and rifapentine which enhanced the half-lives and increased in vitro potency.

3. ADVANCES IN PRECLINICAL DEVELOPMENT

In this review we have tried to present the latest advances made in antitubercular research since last decade in the development of anti-TB agents in preclinical and clinical trials. The status of new antitubercular drugs and their mechanism of action is shown in Table 2, 3 and 4. Currently there are 8 anti-TB agents in preclinical development and 3 anti-TB agents in Good Laboratory Practice toxicity evaluation.

The discovery of entirely new and novel compounds remains challenging task for medicinal chemists. A major advancement in the screening efficacy for novel targets was achieved by researchers shifting from single-enzyme targets to phenotypic screening of the whole bacterial cell. Diarylquinolines (bedaquiline), benzothiazines (BTZ-043 and PBTZ-169) and imidazopyridine amide (Q-203) have been identified through whole bacteria cell. Although many novel compounds are in the preclinical development phase, the pipeline for the early clinical development phase is very rare.
TBA-354, a second-generation nitroimidazole exhibited similar in-vitro anti-tuberculosis activity like delamanid, but shown better activity than PA-824, and slightly improved activity at higher doses in a mouse model of tuberculosis (1000-fold reduction in colony forming unit). Newer nitroimidazole derivatives have shown major improvement in bioavailability in animals as compared to first generation nitroimidazoles suggesting a longer exposure to the drug than with PA-824 or delamanid. Riminophenazines (clofazimine) has reduced duration of treatment of multidrug-resistant tuberculosis, but coloration of skin due to accumulation of drug in fatty tissue and organs is a major side effect. To avoid this problem, TBI-166 was selected from a series of 69 rhiminophenazine derivatives suggesting that it has retained the similar anti-mycobacterial properties.

Q203 is an imidazopyridine moiety containing compound, a new class of drugs that inhibits ATP synthesis more potently than bedaquiline in both aerobic and hypoxic conditions. It has shown tremendous potential against multidrug-resistant and extensively drug resistant strains of *M. tuberculosis* from human beings, and data from animal studies suggest a 100–1000-fold reduction of colony-forming units and a blocking of granuloma formation. PBTZ-169 and BTZ-043 have benzothiazinone scaffold, currently in late stage clinical development. Both drugs act by inhibiting the enzyme decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1) in *M. tuberculosis*. Inhibition of this enzyme prevents the formation of decaprenyl phosphoryl arabinose (a key precursor in the biosynthesis of the cell wall arabinans), which results in cell lysis and bacterial death.

Riminophenazines (clofazimine) has reduced duration of treatment of multidrug-resistant tuberculosis, but coloration of skin due to accumulation of drug in fatty tissue and organs is a major side effect. To avoid this problem, TBI-166 was selected from a series of 69 rhiminophenazine derivatives suggesting that it has retained the similar anti-mycobacterial properties.

Q203 is an imidazopyridine moiety containing compound, a new class of drugs that inhibits ATP synthesis more potently than bedaquiline in both aerobic and hypoxic conditions. It has shown tremendous potential against multidrug-resistant and extensively drug resistant strains of *M. tuberculosis* from human beings, and data from animal studies suggest a 100–1000-fold reduction of colony-forming units and a blocking of granuloma formation. PBTZ-169 and BTZ-043 have benzothiazinone scaffold, currently in late stage clinical development. Both drugs act by inhibiting the enzyme decaprenylphosphoryl-β-D-ribose-2′-epimerase (DprE1) in *M. tuberculosis*. Inhibition of this enzyme prevents the formation of decaprenyl phosphoryl arabinose (a key precursor in the biosynthesis of the cell wall arabinans), which results in cell lysis and bacterial death.

**4. CHEMICAL ALTERATION**

Chemical alteration in a molecule (lead or drug), is an important tool for medicinal chemist to modify the pharmaceutical, pharmacokinetic, and pharmacodynamics properties of a drug. The compound SQ109 has been developed by the molecular hybridization of isoprenyl units, ethambutol pharmacophore, and adamantane moiety. The nitroimidazole analogues TBA-354, PA-824, and OPC-67683 were designed by molecular hybridization using nitroimidazole scaffold. Similarly DC-159a, gatifloxacin, and moxifloxacin were derivatized from the parent nalidixic acid using bioisosterism as molecular modification. The oxazolidinone derivatives PNU-100480 and AZD-5847 were developed using linezolid as parent scaffold by bioisosterism molecular modification tool. The antitubercular agents currently in clinical phase of development which were engineered through the existing scaffolds are shown in table 5.

**5. TUBERCULOSIS VACCINES IN CLINICAL TRIALS**

WHO aims to eradicate TB by 2050, but eradication will be impossible without an effective vaccine. Vaccine provides protective immunity against the acquisition of infection in neonates and infants, and prevents progression from infection to disease or attenuate disease in adults. Vaccines are divided into...
different categories such as recombinant live, viral vectored, recombinant protein or others. BCG (Bacille Calmette Guérin), an attenuated vaccine derived from *Mycobacterium bovis*, is the only licensed TB vaccine, but not recommended in HIV-infected infants. Till now a very substantial research has been carried out over the past decade to develop vaccines against tuberculosis. Existing TV vaccines such as bacille Calmette–Guérin (BCG) is partially effective suggesting an urgent need to develop improved vaccine for tuberculosis. Key components of an ideal TB vaccine include safety and efficacy, effectiveness against pulmonary and MDR-TB, non-interference with other childhood immunizations, easily manufactured formulation on a mass scale which could be stored and administered under feasible conditions. Currently there are 14 vaccine candidates which have entered clinical trials and over 35 candidates in discovery and preclinical development. *Mycobacterium indicus pranii* [Mw; MIP] and *M. vaccae* are in phase III clinical trial. AdAg85A, MTBVAC, and ID93/GLA-SE, and Dar-901 are in Phase 1 clinical trial while Phase II clinical trial vaccines include H56+IC31, Hybrid 4+IC31/ AERAS-404, VPM 1002, Hybrid-14IC31, RUTI, MVA85A/AERAS-485, M72+AS01, and AERAS–402/Crucell Ad35. A number of vaccines are also in preclinical studies such as Mtb [leuCD panCD secA2] (rBCG), HBHA (Protein), HG85A, Hsp (DNA) and so forth vaccine etc. Some of the tuberculosis vaccines in clinical trials are given in table 6. For more information on TB vaccines see references.

6. CONCLUSION

Tuberculosis remains a major cause of death and morbidity worldwide, and concentrated efforts so far have not adequately controlled the epidemic in many parts of the world, especially in the countries of sub-Saharan Africa and parts of Eastern Europe. There are a number of factors responsible to hamper progress towards achieving control of tuberculosis worldwide. i.e absence of availability of proper diagnostic, long duration of treatment, lack of an effective vaccine, emergence of drug-resistant tuberculosis, and weak health systems in resource-poor developing countries. Despite this, there is growing momentum in basic and applied research activity that is starting to yield new diagnostic, treatment, and prevention methods, and now provide grounds for optimism. There are a number of drugs and new compounds are currently under different phases of preclinical and clinical evaluation for the treatment of TB. As we have seen in this review, not only existing antibiotics are being evaluated, but also new molecules are being discovered and tested. We have an important point to note through this review is that most of these new anti-tuberculosis drugs are also effective against MDR *tuberculosis*. Furthermore, some XDR strains have been tested and a small number of patients have been successfully treated. Caution must be taken to avoid improper use of any new drug; otherwise it will lead to drug resistance. This review presents current clinical trial status of all newer molecules in this article. Some of them may reach the last phases of clinical trial, while others could fail to demonstrate acceptable levels of efficacy and safety. It is evident that appreciable number of newer antitubercular agents has been developed in the last decades than before the last 4 decades with different targets. US FDA has approved TMC207 as a part of combination therapy to treat adults with MDR-TB in absence of other alternatives. Furthermore a large number of vaccines are under clinical and preclinical phases of development. The development in the area of newer antitubercular agents and newer vaccines give hope that our vision to eradicate TB might be reached in a few decades.
<table>
<thead>
<tr>
<th>Antituberculosis drug</th>
<th>Class</th>
<th>Genes involved in resistance</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin (1944)</td>
<td>Aminoglycoside</td>
<td>rpsL, rrs</td>
<td>Interferes with biosynthesis of protein through interaction with the 30S subunit of the ribosome.</td>
</tr>
<tr>
<td>Para-aminosalicylic acid (1946)</td>
<td>-</td>
<td>thyAc</td>
<td>Still unknown and an area of investigation.</td>
</tr>
<tr>
<td>Isoniazid (INH, 1952)</td>
<td>Hydrazide</td>
<td>katG, inhA</td>
<td>Mycolic acid synthesis inhibitor, one of the essential components of the mycobacterial cell wall.</td>
</tr>
<tr>
<td>Pyrazinamide (PZA, 1952)</td>
<td>Amide</td>
<td>pncA</td>
<td>Interferes release of pyrazinoic acid, which causes intake of proton and dysfunction of the pH balance of mycobacteria. Recently it has been shown that pyrazinoic acid also targets the ribosomal protein S1, an essential protein involved in the ribosome-sparing process of trans-translation.</td>
</tr>
<tr>
<td>Ethionamide (1956)</td>
<td>Thioamide</td>
<td>inhA, etaA/ethA</td>
<td>Inhibits mycolic acids biosynthesis through the inhibition of inhA.</td>
</tr>
<tr>
<td>Ethambutol (EMB, 1961)</td>
<td>Ethylenediamine</td>
<td>embCAB</td>
<td>Mycobacterial cell wall inhibition by specifically targeting the polymerization of arabinogalactane and lipoarabinomannane.</td>
</tr>
<tr>
<td>Rifampin (RIF, 1970)</td>
<td>Rifamycine</td>
<td>rpoB</td>
<td>Inhibits the mycobacterial RNA synthesis by binding to the β-subunit of the DNA-dependent polymerase.</td>
</tr>
<tr>
<td>Kanamycin (1957)</td>
<td>Aminoglycoside</td>
<td>rrs</td>
<td>Target the small subunit 30S of the ribosome.</td>
</tr>
<tr>
<td>Amikacin (1972)</td>
<td>Aminoglycoside</td>
<td>rrs</td>
<td>Target the small subunit 30S of the ribosome.</td>
</tr>
<tr>
<td>Capreomycin (1963)</td>
<td>Polypeptides</td>
<td>rrs, tlyAb</td>
<td>Target the small subunit 30S of the ribosome.</td>
</tr>
<tr>
<td>Cycloserin (1952)</td>
<td>Oxazolidinone</td>
<td></td>
<td>Triggers peptidoglycan synthesis through D-alanine racemase and D-alanine ligase inhibition.</td>
</tr>
<tr>
<td>Ciprofloxacin (1960s)</td>
<td>Fluoroquinolone</td>
<td>gyrA, gyrB</td>
<td>DNA gyrase inhibitor, which is the sole type II topoisomerase in this organism.</td>
</tr>
<tr>
<td>Ofloxacin (1982)</td>
<td>Fluoroquinolone</td>
<td>gyrA, gyrB</td>
<td>DNA gyrase inhibitor, which is the sole type II topoisomerase in this organism.</td>
</tr>
</tbody>
</table>
Levofloxacin (1992)  

Fluoroquinolone  

gyrA, gyrB  

DNA gyrase inhibitor, which is the sole type II topoisomerase in this organism.  

Table 2: Pipeline for new antitubercular agents

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Structure</th>
<th>Chemical Class</th>
<th>Developer</th>
<th>Target/Mode of action</th>
</tr>
</thead>
</table>
| CPZEN-45  | ![Structure](image1) | Nucleoside antibiotic | Microbial Chemistry Inhibits a novel target WecA  
Research Foundation, Tokyo, Japan  
Lilly TB Drug Discovery Initiative NIAID, IDRI, Lilly | Inhibits a novel target WecA  
30-32. |
| DC-159a   | ![Structure](image2) | Fluoroquinolone | Japan Anti-Tuberculosis Association, JATA  
Daiichi Sankyo Pharmaceutical Co | Under investigation but as other quinolone derivatives, DC-159a possibly affects GyrA activity  
37,38. |
| Q-203     | ![Structure](image3) | Imidazopyridine amide | Qurient Co. Ltd | Specifically targets cytochrome bcl complex of MTB  
39. |
| SQ-609    | ![Structure](image4) | Dipiperidines | Sequlla | Cell wall synthesis inhibitor  
40. |
| TBA-354   | ![Structure](image5) | Nitroimidazole | TB Alliance | Cell wall lipid and protein synthesis inhibitor  
41. |
| TBI-166   | ![Structure](image6) | Riminophenazines antibiotics | Institute of Materia Medica, Targeting the outer membrane & possibly bacterial respiratory chain and ion transporters  
42. |
| SQ-641    | ![Structure](image7) | Capuramycins (Semi-Seqella synthetic Antibiotic) | Sequella | Translocase 1 (TL-1) enzyme inhibitors  
43. |
| PBTZ 169  | ![Structure](image8) | Piperazinobenzothiazinone | Innovative Medicines for Tuberculosis (iM4TB), New York  
for PBTZ169 binds covalently to DprE1, New decaprenylphosphoryl-beta-D-ribose 2-epimerase [44a]. | |
| BTZ043    | ![Structure](image9) | Benzothiazinone | New Medicines for Tuberculosis (NM4TB) | For Acts by inhibition of decaprenylphosphoryl-b-D-ribose 2’-epimerase enzyme which abolishes the formation of decaprenylphosphoryl arabinose, a key precursor required for the synthesis of the cell-wall arabinans, thus provoking cell lysis and bacterial death [44b]. |

Table 3: Pipeline of drugs in Phase II

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Structure</th>
<th>Chemical Class</th>
<th>Resistance</th>
<th>Target/Mode of action</th>
</tr>
</thead>
</table>
| Linezolid | ![Structure](image10) | Oxazolidinone | rRNA 23S mutations | Protein synthesis inhibitor  
44. |
| AZD-5847  | ![Structure](image11) | Oxazolidinone | ----------- | Protein synthesis inhibitor  
44. |
| PA-824    | ![Structure](image12) | Nitroimidazole | Rv0407, Rv3547, Rv3261 and Rv3262 inhibitor  
45. | |
| Rifapentine | ![Structure](image13) | Rifamycin | ----------- | Inhibits DNA dependent RNA polymerase  
46,47. |
| SQ-109    | ![Structure](image14) | Diamine derivatives | Unknown | Cell wall synthesis inhibitor, induces iniBAC operon transcription  
47. |
### Table 4: Pipeline of drugs in Phase III

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Structure</th>
<th>Chemical Class</th>
<th>Resistance</th>
<th>Target/Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPC-67683 (Delamanid)</td>
<td><img src="image" alt="OPC-67683" /></td>
<td>Nitroimidazole</td>
<td>Rv3547 mutations</td>
<td>Cell wall synthesis inhibitor</td>
</tr>
<tr>
<td>Gatifloxacin</td>
<td><img src="image" alt="Gatifloxacin" /></td>
<td>Fluoroquinolone</td>
<td>gyrA mutations</td>
<td>Protein synthesis inhibitor (DNA gyrase)</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td><img src="image" alt="Moxifloxacin" /></td>
<td>Fluoroquinolone</td>
<td>gyrA mutations</td>
<td>Protein synthesis inhibitor (DNA gyrase)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td><img src="image" alt="Ethambutol" /></td>
<td>Nitroimidazole</td>
<td>Rv3547 mutations</td>
<td>Cell wall synthesis inhibitor</td>
</tr>
</tbody>
</table>

### Table 5: Development of Antitubercular Drug By Chemical Alteration

<table>
<thead>
<tr>
<th>Parent drug</th>
<th>Derivatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxazolidone</td>
<td><img src="image" alt="Linezolid" /></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td><img src="image" alt="Nalidixic acid" /></td>
</tr>
<tr>
<td>Nitroimidazole</td>
<td><img src="image" alt="Metronidazole" /></td>
</tr>
<tr>
<td>1,2-Ethlenediamine</td>
<td><img src="image" alt="Ethambutol" /></td>
</tr>
</tbody>
</table>
### Table 6: The Developmental Pipeline for New Tb Vaccines

<table>
<thead>
<tr>
<th>Stage of development</th>
<th>Name of the vaccine</th>
<th>Type of vaccine</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical (GMP)</td>
<td>Mtb [δleuCD panCD secA2]</td>
<td>rBCG</td>
<td>Prime</td>
</tr>
<tr>
<td></td>
<td>HBHA</td>
<td>Protein</td>
<td>Prime, Boost, Post infection &amp; Immunotherapy</td>
</tr>
<tr>
<td></td>
<td>HG85A</td>
<td>DNA</td>
<td>Boost &amp; immunotherapy</td>
</tr>
<tr>
<td></td>
<td>Hsp DNA vaccine</td>
<td>DNA</td>
<td>Boost, Post infection &amp; Immunotherapy</td>
</tr>
<tr>
<td>Phase I</td>
<td>MTBVAC</td>
<td>rBCG</td>
<td>Prime</td>
</tr>
<tr>
<td></td>
<td>Dar-901</td>
<td>WC M. Vaccae</td>
<td>Prime &amp; Boost</td>
</tr>
<tr>
<td></td>
<td>ID93/GLA-SE</td>
<td>Protein/adjuvant</td>
<td>Boost, Post infection &amp; Immunotherapy</td>
</tr>
<tr>
<td></td>
<td>AdAg85A</td>
<td>Viral-vectored</td>
<td>Prime, Boost, Post infection &amp; Immunotherapy</td>
</tr>
<tr>
<td>Phase IIa</td>
<td>H56+IC31</td>
<td>Protein/adjuvant</td>
<td>Prime, Boost &amp; Post infection</td>
</tr>
<tr>
<td></td>
<td>Hybrid 4+IC31/ AERAS-404</td>
<td>Protein/adjuvant</td>
<td>Boost</td>
</tr>
<tr>
<td></td>
<td>VPM 1002</td>
<td>rBCG expressing listeriolysin and urease</td>
<td>Prime &amp; Boost; deletion</td>
</tr>
<tr>
<td></td>
<td>Hybrid-1+IC31</td>
<td>Protein/adjuvant</td>
<td>Prime, Boost &amp; Post infection</td>
</tr>
<tr>
<td></td>
<td>RUTI</td>
<td>Killed WC or Extract</td>
<td>Boost, Post infection &amp; Immunotherapy</td>
</tr>
<tr>
<td>Phase IIb</td>
<td>MVA85A/AERAS-485</td>
<td>Viral-vectored</td>
<td>Boost, Post infection &amp; Immunotherapy</td>
</tr>
<tr>
<td></td>
<td>M72+AS01</td>
<td>Protein/adjuvant</td>
<td>Boost &amp; Post infection</td>
</tr>
<tr>
<td></td>
<td>AERAS-402/Crucell Ad35</td>
<td>Viral-vectored</td>
<td>Boost</td>
</tr>
<tr>
<td>Phase III</td>
<td>Mw [M. indicus pranii (MIP)]</td>
<td>Killed WC or Extract</td>
<td>Immunotherapy</td>
</tr>
<tr>
<td></td>
<td>M. vaccae</td>
<td>Killed WC or Extract</td>
<td>Boost, Post infection &amp; Immunotherapy</td>
</tr>
</tbody>
</table>

### 7. REFERENCES


29. Levine C, Hiasa H, Marian K J. DNA gyrase and topoisomerase IV: biochemical activities, physiological roles during chromosome replication,


42. http://www.newtbdrugs.org/project.php?id=48


Conflict of Interest: None

Source of Funding: Nil