**Antimicrobial Photodynamic Therapy as an Alternative Therapeutic Modality for**

**Drug Resistant Tuberculosis**

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**Introduction**

High tuberculosis (TB) disease burden has been a perennial problem for many countries for centuries.1 As of 2014, there were approximately 9.6 million incident cases of TB worldwide, 1.5 million of which, resulted in deaths.1 Established treatment regimens for Tuberculosis such as the HRZE regimen (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide),2 have proven to be effective in eradicating the disease even in developing countries. However, new strains of drug resistant Tuberculosis have been discovered, they are the Multi-Drug Resistant (MDR) and Extreme Drug Resistant (XDR) Tuberculosis.3 These strains have shown resistance to even second line drug regimens and their incidence has progressively increased since 2003.4 In search of a new alternative mode of treatment, researchers have discovered a new technology called antimicrobial Photodynamic Therapy (aPDT), which is already in use to treat cancerous lesions to date and shows promise for application with Tuberculosis patients.3

**Tuberculosis**

*Background*

Tuberculosis is a global disease problem whose symptoms are severe coughing, fever, and chest pain.4 The number of tuberculosis patients have been decreasing slowly although the incidence remains high. Tuberculosis is a communicable infectious disease, transmitted by airborne droplets, which is mainly caused by *Mycobacterium tuberculosis* (M. tb)*.* Upon inhalation, M. tb can form necrotizing granulomatous inflammation in lungs. The bacteria can be found in patient’s sputum.5

*Pathophysiology of Tuberculosis*

TB, which is acquired by inhalation will travel into the lungs, where it is ingested by macrophages, subsequently forming a granuloma. This granuloma consists of CD4 T-Cells and inflammatory cytokines including IFN-γ, and TNF-α which aid the macrophages in destroying the bacilli. The bacillus which survives will either proliferate within dendritic cells or enter the bloodstream, assuming a dormant state and causing latent infections.4

*Treatment and Management of Tuberculosis*

Control of TB spread requires detection, treatment, hindrance of transmission and increased immunity of susceptible patients. Subclinical asymptomatic TB infections can last from weeks to decades in human hosts, hence, the reservoir for TB is very large. Treatment of TB as established by World Health Organization (WHO), the HRZE regimen (Isoniazid, Rifampicin, Ethambutol and Pyrazinamide) is the most commonly used treatment regimen.6

*Problems with Chemotherapeutic Approach to Tuberculosis Treatment*

TB if left untreated, can cause the death of about 70% of people with positive smear. The incidence of drug resistant strains, MDR and XDR TB has been an ongoing issue since 2003. The case of MDR-TB is now recognized as a major health problem. One of the most common drug-resistance is INH resistance. In 2013, there were 3,5% of MDR-TB of all new TB cases and 9% among them were XDR-TB. Nowadays, the number of cases of XDR-TB where the patient also has second line drug resistant TB is about 24%.4 The number of new cases of multidrug-resistant tuberculosis (MDR-TB) in 2013 was about 480.000 cases, 210.000 of which died. MDR-TB is brought about by a strain of MTB that is resistant to rifampicin and isoniazid (first line drugs which is more effective), while XDR-TB is caused by M. tb strain which also resistant to fluoroquinolone and one of three injectable second-line drugs which are less effective and more toxic (amikacin, kanamycin, capreomycin).7

**Antimicrobial Photodynamic Therapy (aPDT)**

*Background*

Photodynamic Therapy (PDT) is a therapeutic modality that is currently in use to treat various cancer lesions.3 This modality, discovered in the previous century, has been known to exert antimicrobial effects3,8, hence also called Antimicrobial Photodynamic Therapy (aPDT).9 However, poor response of gram negative bacteria, adverse reactions and the discovery of novel antibiotics rendered this technology obsolete.3,8 Recently, the advent of drug-resistant strains of diseases such as methicillin-resistant *Staphylococcus aureus* (MRSA), pathogenic *Vibrio* and *Mycobacterium sp.* calls for an alternative mode of treatment.3,10,11 One proven feature that aPDT has, is the ability to inactivate many microorganisms such as *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli* and *Mycobacterium sp.,* regardless of their drug resistance levels. 3,10,12,13

*Mechanism of Action*

The therapy begins with administration of a particular photosensitizer followed by exposure to an appropriate wavelength of light.3 Light exposure results in the activation of photosensitizers, which leads to the production of reactive oxygen species (ROS), which include singlet oxygen molecules (1O2). The 1O2 molecules are highly electrophilic, thus capable of oxidizing double bonds in biological substrates.14 Subsequently, damage in the cell membrane and DNA occurs, resulting in cell death. aPDT can be effective in treating certain localized bacterial infections by irradiation of infected areas where photosensitizers are applied *in situ*. The main concept of aPDT is to damage target cells whilst avoiding deleterious effects on surrounding normal tissue.12

*Effect of aPDT on DR-TB*

Dramatic increase of drug resistant (DR) strains of M. tb has led to several studies been made regarding the efficacy of aPDT as a therapeutic modality to inactivate this particular bacterium. It has been proved that aPDT is effective in inactivating M. tb in vitro regardless of its drug resistance levels.3 The photosensitizer used in this particular study was radachlorin and DH-I-180-3, with radachlorin showing a greater degree of inactivation.3 This study also showed that application of aPDT in intermittent or repeated intervals resulted in a better outcome compared to prolonged application of aPDT.3

The specific mechanism of photodynamic inactivation of M.tb is not known.3 It is suggested that inactivation of this bacteria is caused by uptake of photosensitizers through pores and porins penetrating mycolic acid and peptidoglycan layers presented in mycobacteria.15,16 This results in the production of reactive oxygen species with its cytotoxic properties, thus killing the bacteria.18

*Potential of Clinical Application of aPDT for the treatment of DR-TB*

Though several *in vitro* studies have been performed, no clinical trials were conducted to assess the potential efficacy of aPDT for the treatment of DR-TB.12 However, a case report concluded that aPDT was successful in eradicating *Mycobacterium marinum* infection in the digital skin17, suggesting its potential role treatment of *Mycobacterium tuberculosis* in vivo. As M. tb is an intracellular bacterium, further studies into aPDT’s ability to inactivate bacilli after infecting monocytes, are required. In addition, further studies are needed to assess the cellular-level pharmacodynamics of photosensitizers and the potential adverse effects of this therapeutic modality.12 The presence of M. tb in the internal surface of lung cavities implies the need of photosensitizers and light to be effectively delivered to the inner surface of the cavity. Visual navigation systems with ultrathin bronchoscopies have been suggested for this approach, potentially facilitating the clinical application of aPDT.12

**Conclusion**

The advent of new drug resistant strains of TB poses a large obstacle in the management of TB patients and calls for an alternative treatment modality. Even though the idea of using aPDT in the treatment of drug resistant strains of TB may still lack concrete evidence and clinical trials, current research and success with *in vitro* samples and case report have shown that this treatment modality is a very promising treatment alternative.

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