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REVIEW

A new solution for a growing problem: Development of novel treatments for strains of drug-resistant tuberculosis

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Abstract

Due to the misuse of antibiotics, drug-resistant strains of tuberculosis (TB) have developed over the last several decades. Current TB medications are often ineffective when it comes to curing patients, therefore new medications are needed to treat these drug-resistant strains of TB. Drugs that target bacterial cell components and interact well with existing TB medications should be considered. Three new medications that should be considered for the use of treating drug-resistant TB are Bedaquiline, PNU-100480, and a topoisomerase inhibitor. By introducing several new medications into the market, drug-resistant TB can be more effectively treated.

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Introduction

Over the last century, the discovery and increased use of antibiotics has helped cure millions of illnesses that were previously untreatable. As the use of antibiotics increased, the number of drug resistant bacteria also increased. As bacteria become resistant to more medications, there are fewer treatment options available to physicians. New antibiotics are needed to treat the growing problem of drug-resistance, but the process of introducing a new antibiotic into the market can take years, or even decades of research and development. Investing in new medications that are less likely to become obsolete due to drug resistance provides a long term solution.

One disease that has seen an increase in the frequency of drug-resistant strains is tuberculosis (TB). TB is the second most infectious killer in the world only behind HIV/AIDS and in 2012 alone roughly 9 million people became infected with TB (World Health Organization 2013). In some countries, the percentage of TB cases that are drug resistant is as high as 70% (World Health Organization 2013). While TB is not prevalent in first world countries, the spread of drug resistant TB in developing countries is cause for concern. The development of new medications to treat drug resistant strains could greatly reduce the occurrence of TB throughout the world. This review outlines several new possible medications that could effectively treat drug susceptible, as well as drug resistant strains of tuberculosis. These medications include Bedaquiline, PNU-100480, and a type II topoisomerase inhibitor which has not yet been developed.

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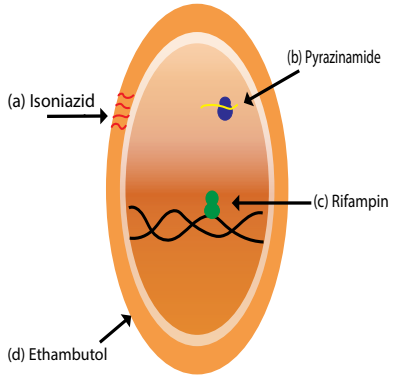

Figure 1. Cellular targets for first-line tuberculosis drugs. (a) Isoniazid interferes with the growth of the cell wall by preventing the synthesis of mycolic acid (red). Mycolic acid makes up a majority of the cell wall. (b) Pyrazinamide interferes with ribosomal proteins (blue) thereby inhibiting protein synthesis. (c) Rifampin prevents synthesis of RNA by inhibiting RNA polymerase (green). (d) Ethambutol disrupts growth of the cell wall leading to increased cell wall permeability. Modified from Mitchison, Nature, 2005.

Mycobacterium tuberculosis
A bacterial species that causes the disease tuberculosis in humans.

Isonaizid
A first-line TB drug that targets the growth of the cell wall by inhibiting the production of mycolic acid.

Rifampin
A first-line TB drug that interferes with the function of RNA polymerase, thereby preventing transcription from occurring.

Ethambutol
A first-line TB drug that causes the cell wall to become more permeable which leads to death of the cell.

Pyrazinamide
A first-line TB drug that interferes with ribosomal binding and prevents translation from occurring.

General Characteristics of *Mycobacterium tuberculosis*

The bacteria ***Mycobacterium tuberculosis*** causes an infection of the lungs called tuberculosis. These bacteria spread easily from person to person through the air when an infected person coughs or sneezes. *M. tuberculosis,* a rod shaped bacteria, has already infected roughly one third of the world's population, with about 10% of those infected having active cases of tuberculosis (TB). The other 90% of TB cases are latent, meaning *M. tuberculosis* is present in the lungs of the patient but the bacteria are not actively dividing so the patient shows no signs of infection. A latent case of TB is more likely to become active in patients who are immune-compromised, especially HIV/AIDS patients, whose immune systems cannot suppress infections. When a case of TB does become active, a patient may exhibit several symptoms including loss of appetite, weight loss, fever, and chills. In the case of pulmonary TB, which is usually confined to the lungs, symptoms include those previously listed as well as coughing and chest pains. When TB spreads to other body systems, it is referred to as extra-pulmonary TB and a patient's symptoms will depend on which system becomes infected.

Current Treatment Options for Drug-Susceptible TB

First line treatments used to treat TB initially include a combination of **Isonaizid** and **Rifampin**. Other first line drugs such as **Ethambutol** and **Pyrazinamide** may be prescribed if necessary. The use of several TB medications at one time is useful for weakening *M. tuberculosis* cells at different cellular targets. Isonaizid, for example, interferes with the growth of bacterial cell walls by preventing the synthesis of mycolic acids, an important component of the cell wall (Figure1). Ethambutol also disrupts the cell wall by making it more permeable which can lead to cell death. In addition to medications that target the bacterial cell wall, Rifampin interrupts the function of RNA polymerase, a transcription enzyme, which prevents the transcription of DNA into RNA (Figure 1). Without the production of RNA, protein products cannot be produced, and TB cells no longer function properly. Lastly, Pyrazinamide interferes with the production of proteins by preventing the binding of ribosomal proteins, thereby preventing translation of RNA (Figure 1).

Treatment plans for TB can last anywhere from six months to a year (Hopewell 1984) and longer treatment plans may be necessary if a patient remains actively infected with TB. If first-line drugs are not effectively treating a patient's TB, there are several second-line prescription medications such as Kanamycin, Capreomycin, and Amikacin that may be used for treatment. Similarly to the first-line drugs, the second-line medications also interfere with cellular components such as ribosomes and structural aspects of the cell wall.

Multi-drug resistant tuberculosis (MDR-TB)
A strain of tuberculosis that is resistant to at least Isonaizid and Rifampin.

Extensively drug resistant tuberculosis (XDR-TB)
A strain of tuberculosis that is resistant to all first-line tuberculosis medications and at least one second-line medication.

Asymptomatic
A condition of showing no symptoms.

Several Causes of Drug Resistant TB

Over time TB may no longer respond to medications and may become drug-resistant. There is a range of drug resistance that is observed among strains of TB and several categories of drug-resistance have been described. One such category is **multi-drug resistant TB (MDR-TB)** which is used to describe strains of TB that are resistant to at least Isonaizid and Rifampin and potentially other first-line medications. Another category of drug-resistance is **extensively drug-resistant TB (XDR-TB)** which describes strains that are resistant to all first-line medications and at least one second-line medication.

There are several causes that result in the development of drug resistant strains of TB. One major cause of drug resistance is prematurely interrupted treatment plans. When a TB treatment plan is not followed through to completion, in other words if the patient is not completely free of *M. tuberculosis* when treatment has stopped, the TB cells that remain are those that were resistant to a shorter duration of the administered medications. These cells can then multiply, resulting in an increased number of drug resistant TB cells within a patient's lungs. If treatment is later resumed, the newly established population of cells will be harder to treat as fewer medications will be effective against the resistant TB cells. The early termination of treatment has greatly increased the extent of drug resistance in many strains of TB and yet it still continues to occur for several reasons. Many of the medications used to treat TB have uncomfortable and even painful side effects such as nausea, nerve pain, headaches, rash, and inflammation of the liver (Gadkowski 2012). Due to these side effects, many patients stop taking their medications without the approval of a physician. Often times a patient may no longer be exhibiting symptoms of TB and will no longer take their medications. Though patients may be **asymptomatic**, there may still be actively dividing TB cells in the patient's lungs which may potentially be drug resistant and can also lead to the redevelopment of TB symptoms for the patient in the future. In countries where expensive medications such as those used to treat TB are not always available, patients may be able to start a treatment plan but they may not be able to complete it due to medication shortages. Drug resistance can occur due to a combination of these factors resulting in the early termination of treatment.

Mechanisms of Drug Resistance in Tuberculosis: Isonaizid Resistance

When the use of antibiotics results in a drug resistant strain of TB, there are usually one or more specific genes in the *M. tuberculosis* genome that have been randomly mutated due to chance. These mutations are then selected for due to the use of antibiotics. For example, TB strains that are resistant to Isonaizid usually have a mutation at the *inhA* promoter (Muller et al. 2013). The *inhA* promoter plays a role in the production of mycolic acids used to structure the cell wall (Morlock et al. 2003). The *inhA* promoter is a target for Isonaizid and when it becomes mutated the medication can no longer bind to the promoter. This results in TB cells that can continue to build cell walls and are considered drug resistant to Isonaizid.

Another example of mutations that lead to drug resistance can be seen in the *rpoB* gene which when mutated may lead to Rifampin resistance (Ocheretine et al. 2014). *RpoB* is a gene that encodes for a subunit of RNA polymerase which is the target of Rifampin (Ocheretine et al. 2014). The result is a mutated RNA polymerase that is not affected by Rifampin which allows the transcription of genes to still occur. Such examples can be seen with the other TB prescription medications, where mutations at one or two genes result in resistance against a particular medication.

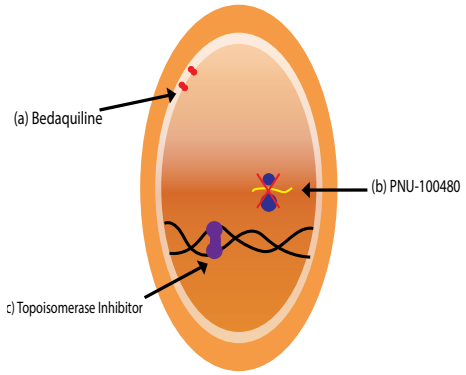

Figure 2. Cellular targets of potential tuberculosis drugs. (a) Bedaquiline inhibits the function of proton pumps (red) used for ATP synthesis. These proton pumps are embedded in the cell plasma membrane. (b) PNU-100480 does not allow the translation initiation complex, which includes a ribosome (blue) and RNA (yellow) to form thereby preventing translation. (c) Topoisomerase inhibitors prevent topoisomerase (purple) from untangling DNA.

Potential New Treatments for Tuberculosis

When considering targets for new medications, highly constrained drug targets are ideal as compared to drug targets that can withstand mutations which are targeted by current TB medications. Medications such as **Bedaquiline** and topoisomerase inhibitors target bacterial components that are highly constrained. Another aspect to consider when investigating new treatment options is drug interactions and safety. If a new medication can be implemented to make current medications more effective, such as **PNU-100480**, it is a better candidate for use then a drug that interacts with adverse side effects such as loss of appetite, nausea, or inflammation of the liver. When taking safety into account, drug targets that are found in bacterial cells and not human cells are ideal. Three new potential treatments that have these characteristics are described in the following sections.

Bedaquiline
A TB drug recently approved by the FDA; Bedaquiline inhibits bacterial ATP synthase which prevents production of ATP.

PNU-100480
A TB drug currently in clinical trials; PNU-100480 inhibits translation so that proteins are not produced.

The Latest FDA Approved TB Medication: Bedaquiline

Bedaquiline was introduced to the market in December of 2012, and was the first TB medication to be FDA approved in 40 years with a new drug mechanism (Mahajan 2013). While Bedaquiline can be used to treat both drug susceptible and drug resistant TB, it is currently used as a last resort on a case by case basis when the other classic TB drugs are not effective. Bedaquiline works by targeting the proton pump that drives ATP synthase, an enzyme used to synthesize ATP (Matteelli et al. 2010), (Figure 2). The drug specifically targets the *atpE* gene which has been found to be highly conserved across many *M. tuberculosis* strains as well as other *Mycobacterium* species (Petrella et al. 2006). The highly conserved nature of the gene, along with the naturally low mutation rate of *atpE*, makes this gene an excellent drug target.

There are several unique characteristics of Bedaquiline that demonstrate why it should be used to treat TB on a regular basis, instead of only as a last resort. First, the efficiency of Bedaquiline surpasses the medications currently used to treat TB. Studies have shown that Bedaquiline has eliminated TB from patients in as little as two months (Lounis et al. 2006). This can be compared to the current TB treatments which can take six months to a year, and perhaps even longer, to cure a patient. By shortening the TB treatment regimen, patients will be more likely to complete treatment and opportunities for mutations to occur in the TB genome will be reduced. Bedaquiline has also been shown to have an effect on non-dividing TB cells (Rao et al. 2008). This differs from many medications that can only affect diving cells such as Isonaizid. Bedaquiline affects non-dividing cells by depleting the low levels of ATP found in these cells which is needed for basic functions (Rao et al. 2008). By eliminating both actively dividing and non-dividing TB cells, Bedaquiline can more quickly

eliminate TB from a patient. Bedaquiline may also have the potential then to treat patients with latent TB, as it targets cells that are not actively dividing.

The potential for a simplified treatment regimen involving Bedaquiline also exists. When administered in vivo, Bedaquiline exhibits a relatively long half-life of 173 hours, when compared to other drugs (Andries et al. 2005). This means that Bedaquiline has the potential to be effective over longer periods of time and could be administered less often. One study found that mice that were given 100mg/kg doses of Bedaquiline once a week were more successfully treated than mice that were given 25mg/kg doses 5 times per week (Veziris et al. 2009). Reducing the number of doses that a patient must take would simplify the treatment regimen of TB and ultimately reduce the cost of treating patients. A shorter treatment plan allows less time for *M. tuberculosis* to become resistant and increases the probability of a patient completing treatment.

The safety of Bedaquiline has also been tested and thus far only mild symptoms have been reported. These symptoms include nausea, diarrhea, dizziness, and a rash, but no side effects have been significant (Diacon et al. 2009). The safety of Bedaquiline can further be explained by differences in the *atpE* homolog found in humans. While the *atpE* gene is highly conserved between Mycobacterium species and eukaryotes, the resulting ATP synthase protein contains a methionine at position 63 in humans, and an alanine at this position in Mycobacterium (Haagsma et al. 2009). This difference of one amino acid renders Bedaquiline unable to affect the ATP synthase activity of human cells thus allowing Bedaquiline to safely treat TB patients.

Based on previous research, Bedaquiline would be most useful if implemented as a second-line TB drug and used to treat MDR-TB and XDR-TB. When tested in combination with several first line drugs, Bedaquiline showed varying efficacy for eliminating TB. When administered along with Rifampin, the effectiveness of Bedaquiline dropped by 50% (Metteelli et al. 2010). However in preclinical trials, when Bedaquiline and Pyrazinamide were paired together to treat TB infected mice the overall effectiveness of the two drugs increased (Ibrahim et al. 2007). Due to the mixed results when combining Bedaquiline with various first-line medications, it is unclear if Bedaquiline should be used as a first-line drug. Bedaquiline may be more useful as a second-line TB medication because it increases the effectiveness of the current second-line medications and could make second-line regimens more efficient (Mitnick et al. 2007). By increasing the effectiveness and efficiency of second-line treatment regimens, cases of MDR-TB and XDR-TB could be more easily treated and cured more quickly.

Medications in Clinical Trials: PNU-100480

Another option for developing new TB treatments is to redevelop currently used drugs and modify them to be effective against drug resistant strains of TB. The drug PNU-100480 is a medication that is currently in clinical trials. It is similar to Pyrazinamide in that it inhibits translation thereby stopping production of proteins but these two medications differ in how they prevent translation. PNU-100480 differs from Pyrazinamide in that it belongs to a family of drugs called oxazolidinones which prevent translation of proteins by preventing the binding of the translation initiation complex (Williams et al. 2009), (Figure 2). Pyrazinamide on the other hand, prevents translation by interfering with ribosome function. In clinical trials, PNU-100480 was effective against both MDR-TB and XDR-TB, which Pyrazinamide can typically no longer treat effectively (Wallis 2011). By examining the prescription medications already used to treat TB and determining how they are deficient, these

medications can be modified in order to treat drug resistant strains of TB.

Medications in the oxazolidinones family, such as Linezolid which is currently used to treat pneumonia, have unsuccessfully treated TB in past studies (Williams et al. 2009). Oxazolidinones have also been shown to cause neurological damage after months of use which made the use of this class of drugs to treat TB unrealistic (Nagiec et al. 2005). However, studies involving PNU-100480 have thus far been promising when it comes to safely and effectively treating TB.

PNU-100480 when compared to Linezolid, can more effectively treat TB and should therefore be considered as a treatment option for TB. In one study PNU-100480 was found to be 15 times more effective than Linezolid when treating TB (Williams et al. 2009). Also, PNU-100480 was easily absorbed by patients even when the medication was not taken with food (Wallis et al. 2011). The ability of a medication to be absorbed in the absence of food would be advantageous in countries where patients may not always have food to eat with their medications.

Unlike most other oxazolidinones, PNU-100480 does not result in harmful side effects. PNU-100480 has been tested in patients at several dosing levels, as high as 1200 mg/day, and no serious side effects were observed (Wallis et al. 2011). It has also been found that PNU-100480 can be safely used in combination with first-line TB drugs (Wallis et al. 2012). In fact, PNU-100480 was shown to increase the effectiveness of first-line drugs two-fold (Williams et al. 2009). By implementing PNU-100480 into the standard first-line treatment plan, patients would be treated more effectively and the time required for treatment would most likely be shorter. PNU-100480 has also been shown to decrease the relapse rate of TB in mice when paired with the first-line drugs. When mice were treated with both PNU-100480 and first-line drugs, most mice were cured after four months with only 35% of mice relapsing (Williams et al. 2009). When mice were treated with only first-line medications, the relapse rate was 90% (Williams et al. 2009). By decreasing the rate of relapse in TB cases, both time and money can be saved. This also decreases the likelihood that drug-resistance will develop by eliminating TB more quickly.

New combinations of medications are also proving to be more effective against TB then traditional treatments. One study used a combination of PNU-100480 and Bedaquiline and compared the effectiveness of these two drugs against that of the first-line drugs currently used. The combination of PNU-100480 and Bedaquiline was found to be more effective at treating TB than the traditional medications (Williams et al. 2012). The ability to pair PNU-100480 with current TB drugs, as well as new and developing drugs, makes it a strong candidate for use in the treatment of TB. Specifically, PNU-100480 could be implemented as a first-line drug until other new drug combinations are fully tested. The lack of serious side effects, unlike those seen with other drugs in the oxazolidinone family, as well as PNU-100480's ability to decrease the rate of relapse demonstrate why PNU-100480 should be used to treat TB.

A New Potential Drug Target: Topoisomerase Inhibitors

A drug target that could potentially be used to treat TB is the **type II topoisomerase** found in bacterial cells. The medications described previously are found to be so effective because they target essential cellular mechanisms. Further investigation to find other essential cellular components to target should be the next step in treating TB. When a gene is not highly constrained evolutionarily, mutations will be more readily tolerated and less likely to be acted on by selection if mutations occur. For example, if a mutation occurs in a gene that is not required for survival, this mutation may be tolerated, in other words

Type II topoisomerase
An enzyme that causes double stranded breaks in DNA in order to reduce the amount of super-coiling in the DNA. This enzyme also reanneals the DNA back together.

the organism can still survive even with the mutation. This mutation can then be passed on to subsequent generations. A gene that is highly constrained may prove to be a more effective drug target and may resist mutations more easily. Using highly constrained genes as drug targets could prevent drug resistance from occurring in strains of TB (Perez et al. 2014). One such drug target is the type II topoisomerase, which has the potential to be inhibited by antibiotics.

Type II topoisomerases aide in the uncoiling of super-coiled DNA by producing double stranded breaks in the DNA, allowing the DNA to unwind, and then re-annealing the DNA strands back together (Perez et al. 2014), (Figure 2). Without relieving some of the super-coiling in DNA, the DNA becomes tightly wound and there is the potential that important DNA sequences will not be accessible for transcription. Loss of transcription results in a loss of protein products needed for cell survival. By picking type II topoisomerases, which are essential for cell survival, as a drug target the risk of drug resistance developing due to a mutation at this gene is reduced. Also, targeting type II topoisomerases in bacterial cells does not affect any enzymes in human cell (Perez et al. 2014), making this target safe for treating TB in humans.

A potential drug candidate that could be used to target topoisomerases is in the quinolones family of antibiotics (Drlica et al. 2008). While most antibiotics are produced by bacteria or yeasts, quinolones are synthetically produced (Perez et al. 2014). An advantage to using synthetically produced antibiotics is that they can be modified more easily than naturally produced antibiotics. This can be useful when aiming for specific drug targets in a cell. The quinolones can be tailored to target specific cellular components based on which species of bacteria is being treated. While there is not currently a TB drug targeted at type II topoisomerases, modified versions of quinolones should be investigated in their ability to treat TB.

Conclusions

By developing new TB drugs that target highly constrained genes and redeveloping prescription drugs currently used to treat TB, drug resistant strains of TB can be more effectively treated. Drugs targeting constrained genes will aide in slowing the development of new drug resistant strains of TB. Redeveloped prescription medications on the other hand could play a role in treating established strains of MDR-TB and XDR-TB. One or even a few new medications will most likely not be enough to treat TB on a global scale. Instead, a combination of many new drugs will be needed in order to effectively treat the growing number of drug resistant strains. By investing in new medications, and investigating novel drug combinations those affected by drug-resistant strains of TB could be cured and perhaps solutions for other drug resistant bacteria species could be discovered as well.

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