Applications
Potential therapeutic applications of the DprE1 inhibitors include:
- Tuberculosis (TB)
- Other mycobacterium associated infections such as *Mycobacterium avium* complex

The Technology
Researchers at the Institute for Molecular Bioscience (IMB) at The University of Queensland (UQ) are developing small molecule inhibitors of decaprenylphosphoryl-β-D-ribose 2′-epimerase (DprE1). DprE1, together with DprE2, catalyzes the epimerization of decaprenylphosphoryl-β-D-ribose (DPR) to decaprenylphosphoryl-β-D-arabinose (DPA), a central precursor for the synthesis of cell-wall arabinans in mycobacteria. Analysis of orthologs has revealed that DrpE1 is essential for the growth of mycobacteria, making it a valuable target for drug development.

1,3-Benzothiazin-4-ones (benzothiazinones; BTZ) are potent inhibitors DrpE1. This new class of drug candidates shows potent activity against *Mycobacterium tuberculosis* (*Mtb*) in cell based assays and *in vivo* studies. Several nitro containing BTZ compounds show minimal inhibitory concentrations (MIC) below 1 ng/mL against *Mtb* H37Rv. As illustrated in Figure 1, BTZ043, the most promising candidate of the BTZ compounds, shows excellent *in vitro* (3 ng/mL), but less efficacy *in vivo* in *Mtb* infected mice compared to existing TB drugs and compounds in development. Nevertheless a recent study reports that several clinical multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB) isolates are susceptible to BTZ043, making it a valuable class of molecule against multi-drug resistant TB.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>CFU red.</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; [μg/mL]</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTZ043</td>
<td>3.3</td>
<td>0.003</td>
</tr>
<tr>
<td>INH</td>
<td>5.6</td>
<td>0.02 – 0.2</td>
</tr>
<tr>
<td>INH+RIF</td>
<td>4.8</td>
<td>0.1 – 2 (RIF)</td>
</tr>
<tr>
<td>INH+RIF+PZA</td>
<td>4.9</td>
<td>0.015 – 0.53</td>
</tr>
<tr>
<td>PA-824</td>
<td>4.6</td>
<td>0.002 – 0.150</td>
</tr>
<tr>
<td>TMC207</td>
<td>4.9</td>
<td></td>
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</tbody>
</table>

**Figure 1.** Comparison of the *in vivo* reduction in lung colony forming units (CFU) for treatment of mice infected with *Mtb* with *in vitro* MIC for BTZ043 and competing drugs.
The research team has undertaken an extensive medicinal chemistry program to develop more potent and more stable analogues of the BTZ compounds with improved in vivo efficacy. The lead molecules from the program occupy a different chemical space and have composition of matter patent protection.

Market Opportunity
The current treatment for TB involves a cocktail of anti-microbial agents for up to 9 months, including isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), ethambutol (EMB) and streptomycin (SM). This prolonged treatment results in poor patient compliance, which has been associated with increasing prevalence MDR-TB and XDR-TB. A 2009 World Health Organisation report estimated 440,000 cases of MDR-TB (3.3% of all new TB cases globally), causing an estimated 150,000 deaths, and that 5.4% of MDR-TB cases were found to be XDR-TB, reported now in 69 countries.

Intellectual Property
National phase applications with composition of matter claims were filed by The University of Queensland in May 2014 to protect the DprE1 Inhibitors and uses thereof.

Commercialisation Opportunities
UniQuest is seeking licensing, investment or collaborative partners to further develop the compounds against TB.

Relevant Publications
