New-generation polymyxins that target multidrug-resistant Gram-negative bacteria. These novel lipopeptide antibiotics have demonstrated superior in vivo efficacy and toxicity over current polymyxin antibiotics.

- Novel lipopeptide antibiotics that target multidrug-resistant Gram-negative bacteria
- Greater efficacy and significantly less nephrotoxicity in animal models than currently available Polymyxin B and Colistin
- Potential for administration via intravenous, inhaled or topical routes

THE CHALLENGE

The World Health Organization has identified antimicrobial resistance as one of the three greatest threats to human health. The world is facing an enormous and growing threat from the emergence of bacteria that are resistant to almost all available antibiotics. There has also been a marked decline in the discovery of novel antibiotics for the treatment of infections caused by Gram-negative pathogens. The Infectious Diseases Society of America lists several highly resistant Gram-negative pathogens as significant emerging pathogens. Numerous hospitals worldwide have experienced outbreaks of infections caused by Pseudomonas aeruginosa, Acinetobacter baumannii or Klebsiella pneumoniae that are resistant to all commercially available antibiotics, except for polymyxins.

Despite the efficacy of polymyxins in treating certain Gram-negative bacterial infections, their use is limited by a narrow therapeutic window and nephrotoxicity. Parenteral administration of Colistin and Polymyxin B is associated with acute kidney injury in up to 60% of patients, limiting the routine use of these agents in treating multidrug-resistant Gram-negative bacteria. However, polymyxins are now being used as the last-line class of antibiotics to treat infections, where all other available antibiotics are inactive.

THE TECHNOLOGY

Using their polymyxin drug discovery platform, researchers from the Monash Institute of Pharmaceutical Sciences have identified a series of proprietary Polymyxin analogues that are active against Gram-negative ‘superbugs’ (Table 1).

The Monash researchers have completed in vivo efficacy and toxicity evaluations of the lipopeptide antibiotics in mouse models. When compared with commercially available Polymyxin B and Colistin, the lipopeptide analogues demonstrate improved antibacterial efficacy (Figure 1) and significantly less nephrotoxicity (Table 2).


THE OPPORTUNITY

Monash seeks a partner to complete preclinical assessment of its series of novel lipopeptide antibacterials, nominate a clinical candidate, and undertake clinical development. The researchers and Faculty of Pharmacy and Pharmaceutical Sciences have extensive academic and industrial experience in medicinal chemistry, optimisation of pharmacokineti/ pharmacodynamics, and in vitro and in vivo evaluations of antibiotics.

Reference


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Table 1: Minimum inhibitory concentrations (MICs) of Polymyxin B and novel lipopeptides against MDR clinical isolates.

<table>
<thead>
<tr>
<th>MIC (µg/mL)</th>
<th>P. aeruginosa</th>
<th>A. baumannii</th>
<th>K. pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymyxin B</td>
<td>1.5</td>
<td>0.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Novel Lipopeptide</td>
<td>0.2</td>
<td>0.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table 2: Assessment of kidney histological damage after treatment (60 mg/kg) with Polymyxin B or a novel lipopeptide in a mouse nephrotoxicity model.

<table>
<thead>
<tr>
<th>Peptide</th>
<th>n</th>
<th>Grading of Kidney Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3</td>
<td>No Grade (no damage)</td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>3</td>
<td>Grade 2 Damage (significant)</td>
</tr>
<tr>
<td>Novel Lipopeptide</td>
<td>3</td>
<td>No Grade (no damage)</td>
</tr>
</tbody>
</table>