Novel Ribosome Inhibitors are Efficacious in a Murine Kidney Infection Model Caused by Staphylococcus aureus MRSA USA300

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Abstract
Background
There is a dearth of novel antibacterial agents to treat serious Gram-positive and Gram-negative infections. Of particular concern are hospital and community-acquired infections caused by methicillin-resistant S. aureus (MRSA). We have used structure-based drug design to generate compounds in three chemical scaffolds targeting the large subunit of the bacterial ribosome. Compound RX-04 dosed subcutaneously demonstrated broad spectrum in vivo activity, further studied in a murine kidney infection model caused by MRSA USA300.

Results
Murine kidney infections were initiated in naïve mice via tail vein injection of S. aureus MRSA USA300. Therapy was administered at 4, 24 and 32 hours post-infection, and kidney were homogenized for bacterial quantification at 44 hours post-therapy. Two dose levels (20 and 200 mg/kg) were tested and the number of colony forming units (cfu) were enumerated. Kidneys from untreated control mice served as a serial control. RX-P724 demonstrated cfu reductions of 4 - 5 log10 cfu compared with untreated controls, while RX-P569 demonstrated cfu reductions of 2.2 - 3 log10 cfu. Vancomycin was used as a positive control compound in these studies; typical log10 cfu seen with this drug are 1 – 2 in this model. Over the time period of this infection (44 hours), the cfu increase in untreated control kidneys is ~3.5.

Conclusions
Eight RX-04 compounds from a novel chemical series have demonstrated efficacy in a murine descending urinary tract infection model caused by MRSA. These results are encouraging for the development of new treatment options for MRSA infections that leave clinicians with few therapeutic options. To address this issue, we have used structure-based drug design to generate compounds in three chemical scaffolds targeting the large subunit of the bacterial ribosome. Each compound is a potential candidate for the treatment of serious Gram-positive and Gram-negative infections.

Table 1

<table>
<thead>
<tr>
<th>Compound</th>
<th>MIC vs. MRSA 11540 (µg/mL)</th>
<th>AUC (µg/hr/mL) at 10 mg/kg sc dose</th>
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</thead>
<tbody>
<tr>
<td>RX-P569</td>
<td>0.125</td>
<td>21.3</td>
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<tr>
<td>RX-P907</td>
<td>0.25</td>
<td>18.5</td>
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<tr>
<td>RX-P724</td>
<td>0.5</td>
<td>20.02</td>
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</tbody>
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References

Acknowledgments
We would like to acknowledge the work of John Kirby and Melissa Leguee in providing the MIC values used in this presentation.

Materials and Methods

Introduction
Antibacterial agents to treat serious Gram-positive and Gram-negative infections often fall short due to bacterial resistance, poor tissue penetration or toxicity, leaving clinicians with few therapeutic options. To address this issue, we have used structure-based drug design to generate novel compounds in three chemical scaffolds targeting the large subunit of the bacterial ribosome. Each compound is a potential candidate for the treatment of serious Gram-positive and Gram-negative infections.