Novel Small-Molecule Inhibitors of Bacterial Lipoprotein Transport Against Enterobacteriaceae

Elena Breidenstein, PhD
20 November 2019
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I am a full-time employee as well as a share and option holder of Summit Therapeutics
Summit’s Approach: Innovation for the Patient
Translating novel science into differentiated products delivered to the patient

**DISCOVER**
- New classes of antibiotics
- Distinctive features and benefits
- Targeted spectrum preserves microbiomes
- Less prone to rapid resistance development

**DEVELOP**
- Clinical trial designs to test for unmet need
- Outcomes show superiority over standard of care
- Health economic measures demonstrate value of improved outcomes

**COMMERCIALIZE**
- Patients offered solution to unmet need
- Physicians have data to switch therapy
- Payors have data showing economic value
- Strong stewardship case to use new drugs
Enterobacteriaceae Infections Represent a Significant Unmet Medical Need

- CRE have been characterized as an urgent threat by the CDC
- Some CRE bacteria have become resistant to almost all available antibiotics

• CRE/ESBL producing Enterobacteriaceae cause a wide range of infections such as UTI/cUTI, bacteremia and HAP

* Data from CDC 2019 Antibiotic Resistance Threats Report
Drug Resistant Enterobacteriaceae Infections Are Rising
A Growing Cause of Healthcare-Associated Infections

<table>
<thead>
<tr>
<th>Healthcare Associated Infection</th>
<th>EU incidence ('000s) †</th>
<th>US incidence ('000s) †</th>
<th>% Enterobacteriaceae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia / Lower Respiratory Tract</td>
<td>861</td>
<td>250</td>
<td>27-30 a,b</td>
</tr>
<tr>
<td>Bloodstream</td>
<td>313</td>
<td>249</td>
<td>19-20 c,d</td>
</tr>
<tr>
<td>Urinary tract</td>
<td>888</td>
<td>562</td>
<td>62-75 e-h</td>
</tr>
</tbody>
</table>


Emerging Antimicrobials and Diagnostics in AMR 2019
November 2019
Distribution of Carbapenemases in Enterobacteriaceae Globally

Logan & Weinstein, The Journal of Infectious Diseases, Volume 215, Issue suppl_1, 15 February 2017, Pages S28-S36
Summit Discovery – Primed for New Mechanism Antibiotic Discovery

The perfect alignment of Strategy and Technology

Phenotypic HTS Screen

Discuva Platform

DDS-04 Series: Enterobacteriaceae

Strategy:
Spectrum
New MOA
Indication

Medicinal Chemistry
Discuva Platform

A combination of technologies and different functional expertise groups drives the Discuva Platform

- Library of mutant engineered bacteria
- Next-generation sequencing
- Genome map of mutation insertions
- Outward-facing promoters
- AbR
- Transposon
DDS-04 is a Novel LolC/E Lipoprotein Transport Inhibitor

HTS Hit

Discuva Platform

LoICDE:
- Essential inner membrane ABC transporter in Gram negative bacteria
- Releases lipoproteins into the periplasm from the bacterial inner membrane
Sequence Homology Gives Enterobacteriaceae Specific Activity

![Graph showing sequence homology and MIC for DDS-04a in various Enterobacteriaceae and other Gram-negatives.](image)

Enterobacteriaceae

Other Gram-negatives

- Escherichia coli
- Shigella sonnei
- Enterobacter cloacae
- Klebsiella pneumoniae
- Serratia marcescens
- Yersinia enterocolitica
- Proteus mirabilis
- Pseudomonas aeruginosa
- Acinetobacter baumannii
- Burkholderia cepacia
- Neisseria gonorrhoea

MIC for DDS-04a (µM)

0 50 100 150 200

0 20 40 60 80 100 120 140 160 180 200

LoIC Sequence Homology (%)
DDS-04 Series Exhibits Potent Activity Against a Globally Diverse Panel of Clinical Isolates

Panel of clinical *E. coli* and *K. pneumoniae* isolates

- Extended-Spectrum Beta-Lactamase (ESBL)
- Carbapenem Resistant Enterobacteriaceae (CRE)
- Fluoroquinolone Resistant (FQR)

<table>
<thead>
<tr>
<th></th>
<th>Range (µg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><em>E. coli</em></td>
<td><em>K. pneumoniae</em></td>
</tr>
<tr>
<td>DDS-04a</td>
<td>0.5 - 2</td>
<td>0.5 - 4</td>
</tr>
<tr>
<td>DDS-04b</td>
<td>0.5 - 1</td>
<td>0.5 - 2</td>
</tr>
<tr>
<td>DDS-04c</td>
<td>0.5 - 1</td>
<td>0.5 - 1</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>8 - 128</td>
<td>32 - &gt;128</td>
</tr>
<tr>
<td>Amoxicillin/Clavulanic Acid</td>
<td>2 - &gt;32</td>
<td>1 - &gt;32</td>
</tr>
<tr>
<td>Trimethoprim/Sulfamethoxazole</td>
<td>&lt;0.5 - &gt;16</td>
<td>&lt;0.5 - &gt;16</td>
</tr>
<tr>
<td>Ceftazidime/Avibactam</td>
<td>0.03 - &gt;32</td>
<td>&lt;0.015 - &gt;32</td>
</tr>
<tr>
<td>Colistin</td>
<td>&lt;0.06 - 4</td>
<td>&lt;0.06 - &gt;8</td>
</tr>
</tbody>
</table>
DDS-04 Displays Low Propensity for Resistance Development

- Frequency of resistance of $10^{-09} - 10^{-10}$ @ 4-16 x MIC
- Rapid bactericidal profile
DDS-04a is Well Tolerated with Exposure at Key Infection Sites *In Vivo*

**IV 40mg/kg**

- **200x MIC** (Kidney: 239,414 ng/g)
- **150x MIC** (Urine: 189,000 ng/mL)
- **25x MIC** (Lung: 24,549 ng/g)
- **15x MIC** (Blood: $C_{\text{max}}$ 16,667 ng/mL)

MIC$_{90}$ UPEC: 1 µg/mL
Three Potential Indications in One Drug

- Respiratory Infection: Pneumonia
- Blood Stream Infection: Bacteraemia/Sepsis
- Urinary Tract Infection

Develop compounds which are oral, single dose, narrow spectrum, target three sites of infection.
**In Vivo Proof-of-Concept Achieved in a Murine UTI Model**

Route/Regimen – IV TID over 3 days

Significant reduction in bacterial burden in the urine compared to vehicle → significant reduction also seen in kidney

**Urine burden @ 96h post-infection**

*E. coli UTI89*
*In vivo* Proof-of-Concept Achieved in an Intraperitoneal Mouse Sepsis Model

Route/Regimen – IV TID over 9 hours

**Significant reduction in bacterial burden in blood compared to vehicle**
In Vivo Proof-of-Concept Achieved in a Murine Pneumonia Model
Route/Regimen – IV TID over 26 hours

Lung burden @ 26h post-infection
*K. pneumoniae* ATCC 43816

Significant reduction in bacterial burden in lung tissue compared to vehicle
### DDS-04: A First-in-Class Enterobacteriaceae Antibiotic Series

Programme Highlights

<table>
<thead>
<tr>
<th>Novel MoA</th>
<th>✓ LoIC/E clinically unexploited (powered by the Discuva Platform)</th>
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<tr>
<td>High Potency</td>
<td>✓ Potent activity against globally diverse clinical strains (Enterobacteriaceae); bactericidal profile</td>
</tr>
<tr>
<td>No Pre-Existing Resistance</td>
<td>✓ Very low propensity for resistance development; no cross-resistance with existing classes of antibiotics</td>
</tr>
<tr>
<td>PK Profile</td>
<td>✓ Drug exposure to key infection sites, including bloodstream, bladder, kidneys and lungs</td>
</tr>
<tr>
<td>Safety</td>
<td>✓ Pharmacological and safety properties that support advancement</td>
</tr>
<tr>
<td>Good <em>in vitro</em> / <em>in vivo</em> Correlation</td>
<td>✓ <strong>Proof-of-Concept achieved in UTI, sepsis and pneumonia in <em>in vivo</em> murine models</strong></td>
</tr>
</tbody>
</table>
Contact Details

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