Drug pipeline for Gram-negative bacteria

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## The antibiotic era

<table>
<thead>
<tr>
<th>1950-60s</th>
<th>1970-90s</th>
<th>2000s</th>
<th>2010s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small spectrum</td>
<td>Broad spectrum</td>
<td>Small spectrum</td>
<td>Small spectrum</td>
</tr>
<tr>
<td>Gram positive</td>
<td>Gram positive</td>
<td>Gram negative</td>
<td>Gram negative</td>
</tr>
</tbody>
</table>

### Golden years of pills and profits

1950-60s

- Natural products

1970-90s

- Medicinal chemistry,
  - Semisynthetic products

2000s

- Target based

2010s

- Natural products?
  - Alternative approaches?

Fixing selected resistance problems

**Average annual NME rate**

- Bacteria
- Virus
- Fungus
- Insect
- Parasite
Small molecules in clinical development Phase 1-3

Old: Analog of used antibacterial class
Novel: New antibacterial class

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Non-β-lactams in clinical development

- Aminoglycoside
- Tetracycline
- Peptidomimetic
- Monoclonal antibody
- Vaccine
- Adjunctive therapies
Aminoglycoside: Plazomicin

- Derived from sisomicin
- Phase 3 (partly publicly funded)
  - Pathogen-specific trial
    - Bacteremia and NAP/VAP caused by CRE
    - Plazomicin + meropenem or tigecycline vs colistin + meropenem or tigecycline
    - All-cause mortality at 28 days + disease-related complications at day 28
    - Superiority vs colistin
    - Individualized patient dosing, PK/PD, TDM
  - cUTI (single trial + Phase 2 data)
- NDA end of 2017
# Aminoglycoside: Plazomicin

## E. coli

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MIC (µg/ml)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIS</td>
<td>AMK</td>
<td>GEN</td>
<td>PLAZO</td>
</tr>
<tr>
<td>ATCC 25922</td>
<td>0.5</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>ANT(2”)-I</td>
<td>64</td>
<td>4</td>
<td>&gt;64</td>
<td>1</td>
</tr>
<tr>
<td>AAC(6’)-I</td>
<td>32</td>
<td>32</td>
<td>4</td>
<td>0.25</td>
</tr>
<tr>
<td>AAC(3)-II</td>
<td>&gt;64</td>
<td>4</td>
<td>&gt;64</td>
<td>2</td>
</tr>
<tr>
<td>APH(3′)-Ib</td>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>AAC(3)-IVa</td>
<td>32</td>
<td>4</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>armA methylase</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>&gt;64</td>
<td>&gt;64</td>
</tr>
</tbody>
</table>

Aminoglycoside: Plazomicin

Aminoglycoside: Plazomicin

Carbapenem-resistant enterobacteriaceae

<table>
<thead>
<tr>
<th>Enzymes produced (no. isolates)</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤0.12 0.25 0.5 1 2 4 8 16 32 64 128 ≥256</td>
</tr>
<tr>
<td>ACHN-940 KPC (12) KPC</td>
<td>1 5 6 1</td>
</tr>
<tr>
<td>SME-1 IMP (13) IMP</td>
<td>1 9 3 1</td>
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<tr>
<td>NDM-1 (17)</td>
<td>1 1 1 1</td>
</tr>
<tr>
<td>VIM (5)</td>
<td>1 3 1 1</td>
</tr>
<tr>
<td>OXA-48 (19)</td>
<td>1 17 1 1</td>
</tr>
<tr>
<td>ESBL + impermeability (10)</td>
<td>1 3 1</td>
</tr>
<tr>
<td>AmpC + impermeability (5)</td>
<td>1 3 2</td>
</tr>
</tbody>
</table>

Tetracyclines: Eravacycline

- Fully synthetic tetracycline
- Phase 3
  - clAI (vs ertapenem), cUTI (vs levofloxacin)
    - iv-oral
  - NDA 4Q/2015, MAA 2Q/2016
- Partly publicly funded
- Gram-positive, Enterobacteriaceae, Acinetobacter
- S. aureus: not effected by NorA or MepA efflux pumps
### Tetracyclines: Eravacycline

E. coli expressing recombinant major tetracycline resistance genes

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (μg/ml) for E. coli strain expressing:</th>
<th></th>
<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>lacZ</td>
<td>tet(M)</td>
<td>tet(K)</td>
<td>tet(A)</td>
<td>tet(B)</td>
</tr>
<tr>
<td>Eravacycline</td>
<td></td>
<td>0.063</td>
<td>0.063</td>
<td>0.031</td>
<td>0.25</td>
<td>0.063</td>
</tr>
<tr>
<td>Tigecycline</td>
<td></td>
<td>0.063</td>
<td>0.13</td>
<td>0.063</td>
<td>1</td>
<td>0.063</td>
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<tr>
<td>Minocycline</td>
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<td>0.5</td>
<td>64</td>
<td>1</td>
<td>8</td>
<td>16</td>
</tr>
<tr>
<td>Doxycycline</td>
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<td>2</td>
<td>64</td>
<td>4</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>2</td>
<td>128</td>
<td>128</td>
<td>&gt;128</td>
<td>&gt;128</td>
</tr>
</tbody>
</table>


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Peptidomimetic

- POL 7080
- Protein epitope mimetic of AMP protegrin I, synthetic cyclo-peptide targeting outer-membrane biogenesis of LPS
- Pseudomonas specific
- Phase 1 completed
Monoclonal antibody

- **Panobacumab**
  - Human IgM mAb against the O-polysaccharide of P. aeruginosa serotype O11
  - Phase 2

- **Aerucin**
  - Human mAb binds the polysaccharide alginate on the cell surface of P. aeruginosa
  - Phase 1

- **MEDI3902**
  - Serotype-independent human mAbs, binds three distinct epitopes of P. aeruginosa Psl (exopolysaccharide, host cell attachment and formation and maintenance of biofilms)
  - Phase 1

- **KB001**
  - anti-PcrV humaneered, PEGylated monoclonal antibody fragment against P. aeruginosa
  - Failed in Phase 2 in CF
Vaccines

- **P. aeruginosa antigens**
  - LPS, outer membrane proteins, extracellular proteins, flagella, pili, exotoxins
  - Killed whole cells and live attenuated P. aeruginosa

- **IC43**
  - Hybrid molecule of two of the outer membrane proteins of P. aeruginosa (OprF and OprI)
  - Phase 2: seroconversion at day 14 as determined by OprF/I-specific IgG antibody titer
  - Phase 2/3: ventilated ICU patients, vaccinated at hospital admission and at particular risk of life threatening Pseudomonas infections
Adjunctive and other treatments

- Phages
  - Lytic bacteriophages
  - Bioengineered phages
    - Enzymes derived from phages (eg endolysin)
- Microbiome
- Antivirulence
-Persisters
- Potentiators
- Resistance mechanism targeting
β-Lactamase Inhibitors

Phase 3
Phase 2
Phase 1
Preclinical
Discovery

Class ACD
Class B
Summary

- Gram-negative R&D pipelines
- Mainly fixing problems of old classes
- Antibiotics are a common good
- New approaches are needed
Developing new economic models to incentivise antibiotic R&D + researching and advocating their appropriate use