Targeting a Single Species: *Acinetobacter baumannii*

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Disclosure: Full time employee of Entasis Therapeutics

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Infections caused by *Acinetobacter baumannii* are a significant unmet medical need

- One of the six ESKAPE pathogens
- Increasingly recognized as important cause of severe infections
  - Particularly in compromised hospitalized patients
- *A. baumannii* is a significant public health concern
  - “Critical” on the 2017 WHO Priority Pathogens List
  - “Serious threat" in the 2013 U.S. CDC’s “Antibiotic Resistance Threats”
- *A. baumannii* is a significant global pathogen
  - 60 – 100,000 infections in the U.S. per year
  - ~130,000 in EU5 per year
- Common infection sites
  - Blood stream, lung, urinary tract, and skin
- Mortality rate ~40% with current therapies

<table>
<thead>
<tr>
<th>ESKAPE Pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td>E: <em>Enterococcus faecium</em></td>
</tr>
<tr>
<td>S: <em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td>K: <em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td><strong>A: Acinetobacter baumannii</strong></td>
</tr>
<tr>
<td>P: <em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td>E: <em>Enterobacter</em> spp.</td>
</tr>
</tbody>
</table>
There is growing concern about multi-drug resistant (MDR) *Acinetobacter* ...

... Resistance to polymyxins and tigecycline is now well reported, and a truly pan-drug-resistant (PDR) strain has been described.

Paterson DL, Harris PNA. CID 2015;61(2):155
Spellberg B, Bonomo RA. Crit Care Med. 2014;42(5):1289

... As resistance rates continue to rise, clinicians will increasingly encounter infections caused by carbapenem-resistant *Acinetobacter*. The current data underscore the lethality of infections caused by these strains.
Evolution of antimicrobial resistance in *A. baumannii*

<table>
<thead>
<tr>
<th>Period</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960’s-1970’s</td>
<td>β-lactams</td>
</tr>
<tr>
<td>End of 1970’s</td>
<td>Evolving resistance to aminoglycosides and β-lactams</td>
</tr>
<tr>
<td>1980’-1990’s</td>
<td>The era of the carbapenems</td>
</tr>
<tr>
<td>1990’s-2000’s</td>
<td>Sulbactam provides an alternative</td>
</tr>
<tr>
<td>Today</td>
<td>Multi-drug resistance common Colistin and/or tigecycline often drug(s) of last resort</td>
</tr>
<tr>
<td>The future</td>
<td>??????</td>
</tr>
</tbody>
</table>

Doi Y *et al*. Semin Respir Crit Care Med 2015:36 85.
Carbapenem-resistance in *A. baumannii* is increasing in the US

And carbapenem-resistance in *A. baumannii* is also a major problem in Europe

% of invasive *Acinetobacter* spp. isolates resistant to carbapenems (2015)

European Centre for Disease Prevention and Control. Stockholm: ECDC; 2016
Globally, ~ 60% of A. baumannii isolates are carbapenem resistant

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of Isolates</th>
<th>% Resistant to imipenem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
<td>398</td>
<td>57.6%</td>
</tr>
<tr>
<td>Europe</td>
<td>1229</td>
<td>64.1%</td>
</tr>
<tr>
<td>Latin America</td>
<td>299</td>
<td>75.9%</td>
</tr>
<tr>
<td>Middle East/Africa</td>
<td>189</td>
<td>73.6%</td>
</tr>
<tr>
<td>North America</td>
<td>235</td>
<td>54.0%</td>
</tr>
<tr>
<td>All Regions</td>
<td>2350</td>
<td>64.2%</td>
</tr>
</tbody>
</table>

Derived from Entasis Therapeutics-sponsored surveillance studies
To restore β-lactam activity, inhibition of Classes A, C and D β-lactamases will be required

- Whole-genome sequencing of 84 recent multi-drug resistant A. baumannii strains
  - Demonstrates the complexity of β-lactamase content in A. baumannii

Entasis Therapeutics data on file
Sulbactam-ETX2514 (ETX2514SUL) is in clinical development as a pathogen-specific drug to treat *Acinetobacter baumannii* infections

- **Sulbactam**
  - A β-lactam that is widely used as a β-lactamase inhibitor in the combination product Unasyn™
  - Has intrinsic antibacterial activity against *A. baumannii*

- **ETX2514**
  - A novel, non-β-lactam, β-lactamase inhibitor
    - Broad potent inhibitor of Class A, Class C, and Class D β-lactamases

- **ETX2514 restores the *in vitro* and *in vivo* activity of sulbactam against contemporary multi-drug resistant *A. baumannii***
  - Sulbactam       \( \text{MIC}_{90} = 32 \text{ mg/L} \)
  - Sulbactam + ETX2514 \( \text{MIC}_{90} = 2 \text{ mg/L} \)
ETX2514SUL demonstrates >95% susceptibility against *A. baumannii* at a breakpoint of 4 mg/L

<table>
<thead>
<tr>
<th>ETX2514SUL MIC (mg/L)</th>
<th>≤0.06</th>
<th>0.12</th>
<th>0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>&gt;64</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 N=195</td>
<td>Cumulative %</td>
<td>1</td>
<td>3.1</td>
<td>13.8</td>
<td>41.5</td>
<td>65.6</td>
<td>89.7</td>
<td>96.9</td>
<td>97.9</td>
<td>99.5</td>
<td>100</td>
</tr>
<tr>
<td>2012 N=209</td>
<td>Cumulative %</td>
<td>0</td>
<td>0.5</td>
<td>2.9</td>
<td>20.1</td>
<td>46.9</td>
<td>79</td>
<td>98.6</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>2013 N=207</td>
<td>Cumulative %</td>
<td>0</td>
<td>0</td>
<td>4.3</td>
<td>15.9</td>
<td>43.4</td>
<td>73.8</td>
<td>96.5</td>
<td>97.5</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>2014 N=1131</td>
<td>Cumulative %</td>
<td>1</td>
<td>1.6</td>
<td>7.8</td>
<td>27.9</td>
<td>63.7</td>
<td>88.9</td>
<td>99.6</td>
<td>99.6</td>
<td>99.7</td>
<td>100</td>
</tr>
<tr>
<td>2015 N=202</td>
<td>Cumulative %</td>
<td>0</td>
<td>1.0</td>
<td>7.4</td>
<td>43.1</td>
<td>78.7</td>
<td>97.0</td>
<td>99.5</td>
<td>99.5</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Derived from Entasis Therapeutics-sponsored surveillance studies
Sulbactam-ETX2514 is under development as a pathogen-specific drug.

The challenges!

- Identification of patients with *A. baumannii* infections
  - Represent ~2% of hospitalized Gram-negative infections
- Patients are “sick”
  - Usually hospitalized
  - Generally compromised but not immunocompromised
  - Often in ICUs
  - Generally receiving broad spectrum coverage
  - Patients may have renal impairment
- ~40-50% of patients have pulmonary infections

➢ HOW DO WE TRANSLATE THIS INTO A DEVELOPMENT PROGRAM?
Identification of patients with *A. baumannii* infections

How can we enrich for what is important?

- **What is the target of a new therapy**
  - The unmet need = multi-drug resistant pathogens

- **Although *A. baumannii* infections are relatively uncommon**
  - Multi-drug resistance is very common
  - Routine microbiology can identify *A. baumannii* within 48 hours

  ➢ We can “enrich” for multi-drug resistance by allowing ≤48-hours of prior therapy

- **Prior knowledge of *A. baumannii* is critical before enrollment**
  - BUT prior knowledge of susceptibility is not
    - ~60% will be multi-drug resistant

- **A rapid “bed-side” diagnostic to enrich enrollment and minimize prior antimicrobial therapy would be helpful but is not essential**
Identification of patients with *A. baumannii* infections
Where to find the patients?

- **Focus on infections where *A. baumannii* is more common**
  - Hospital acquired/ventilator acquired bacterial pneumonia
    - ~5-10% of cases in US
- **Focus on geographies where *A. baumannii* is more common**

Chung DR et al. Am J Crit Care Med 2011, **184**:1409
Enrollment of “sick” patients with significant co-morbidities
Understand pulmonary penetration and renal dose adjustment early

- Patients with *A. baumannii* infections have complex medical issues
- Need substantive preclinical efficacy data prior to clinical studies
  - Establish PK targets likely predictive of efficacy
  - Establish clinical dose using robust modelling of Phase 1 PK and preclinical PD targets
- While establishing Phase 3 readiness
  - Generate a limited amount of safety data in “relatively” healthy patients
    - Provides a baseline to review safety data in much sicker population
How do you establish efficacy?

• An event-driven study based on multidrug resistant pathogens
• Enrolling patients with proven *A. baumannii* infections
• Focusing on most common infections; i.e. lung and/or bloodstream
  – Allow patients with other infections into a parallel non-comparative arm to collect supportive data
• In a non-inferiority comparison against a standard-of-care regimen
  – Test superiority if non-inferiority met
• Utilizing a hard endpoint; e.g., 28-day mortality
  – Comparator regimen ~40% mortality
  – No treatment ~80% mortality
  – Proposed non-inferiority margin 20%

➢ Require ~200 patients to provide 118 patients with multi-drug resistant infections
  – 80% power with a two-sided 95% CI assuming 40% mortality in the comparator group and 35% mortality in the experimental group
What might a NDA package look like?
Proposed key elements

- A strong microbiology package
- Strong evidence of *in vivo* efficacy in established and informative murine infection models
- Robust demonstration of PK/PD parameters based on *in vitro* hollow fiber/chemostat models and *in vivo* murine infection models
- Establish dose for Phase 2 and Phase 3 based on high probability of target attainment using robust modelling of preclinical and clinical data
- A safety data base of ~300-400 patients/subjects
  - Consistent with FDA guidance documents
- Demonstrate efficacy compared to standard-of-care in a Phase 3 non-inferiority study
  - Comprehensive justification of non-inferiority margin from published literature

➢ It’s not easy but it is achievable!