Cloudbreak: Antibody-Drug Conjugates for Treatment of MDR Gram-Negative Bacterial Infections

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Advantages of antibody Fc-drug conjugates (ADCs)

1. **Direct kill:** Novel targeting moieties (TMs) tightly bind LPS and kill bacteria - KAPE spectrum
2. **Immunomodulatory:** Fc recruits and initiates an innate immune system response
3. **Potentiation:** Enhances permeability of standard of care therapeutics to provide additional efficacy
4. **Superior PK/ADME:** Antibody-like PK, receptor mediated transport to lung, limited kidney exposures
5. **Protection from septic shock:** Attenuation of sepsis response through LPS scavenging
Additional considerations of Cloudbreak ADCs

- Non-cleavable linker between TM and Fc:
  
  **No dissociation = Prolonged half-life**

- Optimization of **drug to antibody Fc ratio (DAR):**

(DAR optimization ongoing)
Criteria to select Fc type?

<table>
<thead>
<tr>
<th></th>
<th>IgG1</th>
<th>IgG2</th>
<th>IgG3</th>
<th>IgG4</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of total IgG</td>
<td>60</td>
<td>30</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Half-life (days)</td>
<td>21</td>
<td>21</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Complement fixation</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
</tr>
<tr>
<td>Monocyte/PMN affinity</td>
<td>+++</td>
<td>+</td>
<td>++++</td>
<td>+</td>
</tr>
</tbody>
</table>

Human Fc conjugates in mouse efficacy models?

(Human IgG1 is well recognized by mouse effector cells)
ADCs bind, permeabilize, and synergize with SOC agents

- ADCs are designed as mono-therapeutics

Synergy with existing therapeutics is an additional benefit

(e.g. azithromycin; AZM)
## MIC comparison of two distinct ADC classes

<table>
<thead>
<tr>
<th>Strain</th>
<th>Colistin</th>
<th>ADC 07a</th>
<th>ADC 08b</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>E. coli</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 25922</td>
<td>0.4</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>64X-1 (pmrB)</td>
<td>14</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td>AR 0349 (mcr-1)</td>
<td>3.5</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>MMX7746</td>
<td>0.9</td>
<td>ND</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>P. aeruginosa</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAO1</td>
<td>0.9</td>
<td>&gt;3.5</td>
<td>&gt;1.9</td>
</tr>
<tr>
<td>LES 431</td>
<td>0.2</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>A. baumannii</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AB5075</td>
<td>0.4</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>ATCC 19606</td>
<td>0.9</td>
<td>0.9</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>K. pneumoniae</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATCC 10031</td>
<td>0.4</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>ATCC 43816</td>
<td>0.2</td>
<td>3.5</td>
<td>1.0</td>
</tr>
<tr>
<td>MMX6951</td>
<td>&gt;110</td>
<td>&gt;3.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- **Potency increase evident with 2nd generation ADC**
- **Favorable resistance frequencies across KAPE spectrum**
Engagement of the innate immune system by ADCs

- Significant MIC activity under physiologically relevant conditions
  - Decreased MIC in blood suggests immune engagement
  - Inactivation of complement reduces ADC potency in blood (*data not shown*)
Engagement of the innate immune system by ADCs

- Activation of neutrophils by ADCs = **Enhanced potency**

- Multiple studies confirming immune involvement
  - Phagocytic killing assays
  - C3b deposition by flow cytometry
  - Aglycosylated Fc controls
**MICs and immune activation translate to in vivo efficacy**

In vitro → Ec Bacteremia → Ab Pneumonia → Pa Pneumonia → Intra-abdominal (IAI) → Endotoxemia

Single dose of ADC @ T+1 hours

*E. coli* 25922

**ADC 08b Dose Response (day 3 survival)**

- Colistin (0.3)
- ADC 08b (50)
- (25)
- (12.5)
- (6.25)
- PBS

% Survival

08b/COL MW = ~57

- ✓ In vivo efficacy with therapeutic dosing, and expected dose response
MICs and immune activation translate to in vivo efficacy

- Screening of bacteremia active compounds for lung efficacy

- Full protection with a single ADC dose

- Also efficacious in a *P. aeruginosa* lung model
ADCs potently bind and neutralize LPS

Lipopolysaccharide (LPS)

Initiation of a dysregulated host response to infection

Sepsis, characterized by life-threatening organ dysfunction

Inhibition of LPS signaling (nitric oxide)

✅ ADCs are more potent than colistin at immune silencing LPS
ADCs are active in endotoxemia models

- D-galactosamine sensitized model of endotoxemia

**LPS sensitivity:**

<table>
<thead>
<tr>
<th>Species</th>
<th>mg/kg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humans</td>
<td>0.015</td>
</tr>
<tr>
<td>Rabbits</td>
<td>0.02</td>
</tr>
<tr>
<td>Dogs</td>
<td>3</td>
</tr>
<tr>
<td>Rats</td>
<td>7</td>
</tr>
<tr>
<td>Mice (D-GalN)</td>
<td>0.01</td>
</tr>
<tr>
<td>Rhesus</td>
<td>12.5</td>
</tr>
</tbody>
</table>

*LD_{50/100} or shock

✓ Full protection with a single ADC dose

![Graph showing endotoxemia results]

Colistin: IP, T-1 & T+3 hours (mg/kg)
CTC-07a: IV, T-1 hour (mg/kg)
ADCs are active in endotoxemia models

- Dose response in a sensitized mouse model of endotoxemia

IV dosing of compounds @ T-1 hour
18 ng *E. coli* 0111:B4 LPS (IP)
(mg/kg)

- Identical results in neutropenic mice
- 3rd generation ADCs efficacious at 1 mg/kg
- Protective against multiple LPS types:
  - *K. pneumoniae*
  - *A. baumannii*
  - *P. aeruginosa*
  - *E. coli* (3 LPS types)
  - *S. marcescens*
  - *P. mirabilis*
  - *N. gonorrhoeae*

*Screened to date*
Summary and Future directions

- **Properties of Cidara’s 1st and 2nd generation ADCs**
  - Coverage of KAPE pathogens, including colistin-resistant strains
  - Efficacy in multiple infection models
  - Demonstrated engagement of the innate immune system
  - Protection against sepsis by neutralizing LPS

- **3rd generation ADCs being evaluated, so far demonstrating:**
  - Increased potency
  - Improved half-life

- **Models of infection with significant LPS involvement being developed:**
  - Cecal Ligation and Puncture (CLP)
  - *A. baumannii* lung model (sepsis-dominant mortality)
Acknowledgements

- a supportive management team

- an innovative and dedicated R&D team
  - Chemistry department
  - Immunology department
  - In vivo team
  - Microbiology department
  - Protein Chemistry department