Development of Non-Traditional Therapies for Bacterial Infections
Clinical Pharmacology Considerations

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Workshop on Developing Non-Traditional Therapies for Bacterial Infections
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Disclaimer

• The content of this presentation reflects the opinions of the speaker and does not necessarily represent the official position of CDER, the Agency, or the Federal Government.
# Types of Non-Traditional Antibacterial Therapies

**Products that exhibit direct bacterial effect and can be used as monotherapies**

<table>
<thead>
<tr>
<th>Example of targets</th>
<th>Types of drugs</th>
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<tbody>
<tr>
<td>Bacterial cell membrane</td>
<td>Lysins; Lantibiotics; Peptides; Antibody-Antibiotics conjugate</td>
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Conventional MIC-based PK/PD targets may be applied for some of these products

**Products that do not have direct bacterial effect but enhance efficacy of SOC antimicrobials in adjunctive therapies**

<table>
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<th>Functions to enhance Abx effect</th>
<th>Examples of targets</th>
<th>Types of drugs</th>
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</table>
| Restore                         | β-lactamase; Efflux pump | Small molecules; **Biologics & peptides:**  
  - Peptides  
  - Lysins  
  - mAbs  
  - Recombinant proteins |
| Augment                         | Virulence factors (e.g., toxins); Immune factors (e.g., CD28) |  |
| Prevent resistance              | Gut β-lactams; Efflux pump |  |

**MIC-based PK/PD targets are not relevant for most of these drugs**

SOC: standard of care; Abx: antibiotics; mAbs: monoclonal antibodies

*Non-traditional therapies (NTTs) span a variety of products; the presentation will focus on biologics & peptides*
Pharmacokinetic (PK) Considerations

- **Differences in PK behaviors were observed in infected patients vs. healthy subjects**
  - Faster clearance and shorter half-life for some mAbs in infected patients
  - Slower clearance and higher exposures for some peptides in infected patients
  - PK differences in subset of patients

- **Immunogenicity is observed in most NTT biologic & peptide drugs**
  - Higher positive anti-drug antibody (ADA) rate for some lysins following systemic administration
  - Monitor immunogenicity across entire drug development program
  - Develop neutralizing antibody assay, if needed

- **Understanding the drug’s tissue distribution is important**
  - Multiple barriers may exist for biologic & peptide drugs to distribute to the site of infection

Immunogenicity Guidance for Industry:
- Immunogenicity Assessment for Therapeutic Protein Products (2014)
- Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products (2016)
Pharmacodynamic (PD) Considerations

• **Evaluation of mechanism-based PD biomarkers in infected patients**
  – MIC-based PK/PD approach applies to limited NTTs
  – For some peptides with short half-life (~5 min), assessing the long-lasting PD effect (~72 hr) is critical
  – Examples of mechanism-based PD biomarkers: binding of antibody to antigen (e.g., anti-toxin neutralizing antibody when targeting toxins), opsonophagocytic killing effect when targeting exopolysaccharide on bacterial cell surface

• **Determination of clinically relevant downstream effects in patients**
  – For example, effect of immunomodulators on the level of cytokines
  – Impact of NTTs on the antibacterial effect of SOC antibiotics in adjunctive therapy

• **Assessment of clinical PK/PD relationship to support dose selection**
Dose Selection

• **Dose selection based on pre-clinical PK/PD data may not be sufficient**
  – Pre-clinical PK/PD information is useful for Phase 1/2 dose selection
  – PK/PD results from patients are preferred for Phase 2/3 dose selection

• **Conduct dose ranging studies to facilitate dose selection**
  – Consider evaluating multiple dose levels, and multiple dose ratios in combination therapy
  – Determine mechanism-based and clinically relevant PD effects

• **Perform exposure-response (E-R) analyses to assist dose selection**
  – PK/PD relationship
  – Exposure-efficacy relationship
  – Exposure-safety relationship
  – Drug exposure at the site of infection may be more informative for E-R analyses
Additional Clinical Pharmacology Considerations

Most current NTTs are at the early development stage; Clinical Pharmacology studies needed for NTTs should be assessed on a case-by-case basis

- **Drug-drug interaction (DDI) studies**
  - Clinical DDI assessments in combination therapies
  - Therapeutic protein DDI for cytokine or cytokine modulators (e.g., immunomodulators)

- **Effect of hepatic or renal impairment on the PK of NTT biologic & peptide drugs**
  - Hepatic impairment usually does not affect PK of mAbs, with some exceptions
  - Renal impairment may alter PK of therapeutic proteins with molecular weight <69 kDa

- **Effect of NTT biologic & peptide drugs on QTc interval**
  - mAbs usually are not associated with clinically meaningful effect on QTc interval
  - Further assessments may be needed for other biologic & peptide drugs

- **Other Clin Pharm studies on a case by case situation**
Challenges

• **Understand the disposition of NTTs in infected patients**
  – Characterize immunogenicity and its impact on PK/PD, safety, and efficacy
  – Determine drug distribution to the infected tissues
    • Problems of accessibility and representation of tissue samples

• **Understand the drug effect of NTTs to select the dose for Phase 3 studies**
  – Identify appropriate PD biomarkers for non-traditional therapies
  – Understand the clinically relevant pharmacological effects of NTTs in affecting the antibacterial activity of concomitant antibiotics
  – Link pre-clinical PK/PD data to humans when lacking human PK/PD data
    • Phase 2 dose selection of most current NTTs under development are based on in vitro or animal PK/PD data