Microbiology Considerations in the Development of Nontraditional Therapies for Bacterial Infections

Kalavati Suvarna, Ph.D.
Division of Anti-Infective Products
Office of Antimicrobial Products
Microbiological Evaluations

- Mechanism of Action
- Spectrum of Activity
- Resistance Development
- Interactions with other antibacterial drugs
- *In vivo* activity
Mechanism of action

Mechanism of Action Known
- ANTIBODIES
- LYSINS
- ANTIMICROBIAL PEPTIDES
- ANTIVIRULENCE PRODUCTS
- ANTIRESISTANCE PRODUCTS

Mechanism of Action is Unknown
- IMMUNOMODULATORS
- MICROBIOTA MODIFIERS
  Drug inactivators/adsorbers
Spectrum of Activity

- Pathogen specific or narrow spectrum or broad spectrum
  - antigen variability (e.g. antibodies/lysins)
- No MIC assays (e.g. antibodies, biofilm disruptors, immunomodulators)
- MICs may not be predictive and may need standardization (e.g. lysins, antimicrobial peptides)
- No effect on the pathogen (e.g. normal flora assessment, measurement of host immune response, degradation of drug)
Resistance Development

• Mutants with change in the epitope/antigenic drift not studied- most antibodies are developed as single dose

• Traditional growth inhibition studies with log phase cultures may need to be modified (e.g. lysins)

• What other methodologies should be developed to better understand resistance development to non-traditional therapies?
Interactions with Traditional Antibacterial Drugs

• Time-kill assays (static or dynamic) for products with MIC
• Animal models used to show effect of combination versus single agent
• Biochemical/Biophysical assays – relation to clinical effect not known
**In vivo Activity (Animal Models)**

- Animal models of pneumonia, endocarditis, sepsis, thigh infection, catheter implant, systemic infections have been used for non-traditional therapy evaluation
- Immunocompetent and immunocompromised animals
- May not be predictive: host-specific immune evasion mechanisms/virulence factors produced by target bacteria
Challenges

Design and Interpretation
• Design of the functional assay and characterization of activity when the mechanism of action is not well understood
• Interpretation of functional assay as it relates to characterization of the upstream effects
• Exploratory microbiome data

Limited Characterization
• Potential for resistance development
• Interactions with traditional antibacterial drugs used in combination or as standard of care
Challenges

Translation of preclinical data to clinically relevant data

• Lack of predictive animal models for antibody class
• Impact of natural levels of antibodies to pathogen of interest
• Impact of neutralizing antibodies
• Impact of heterogeneous populations and changes in target/virulence factor expression
• Impact of redundant effector functions
• Activity at the site of infection/intracellular activity