Microbiology Considerations in the Development of Nontraditional Therapies for Bacterial Infections

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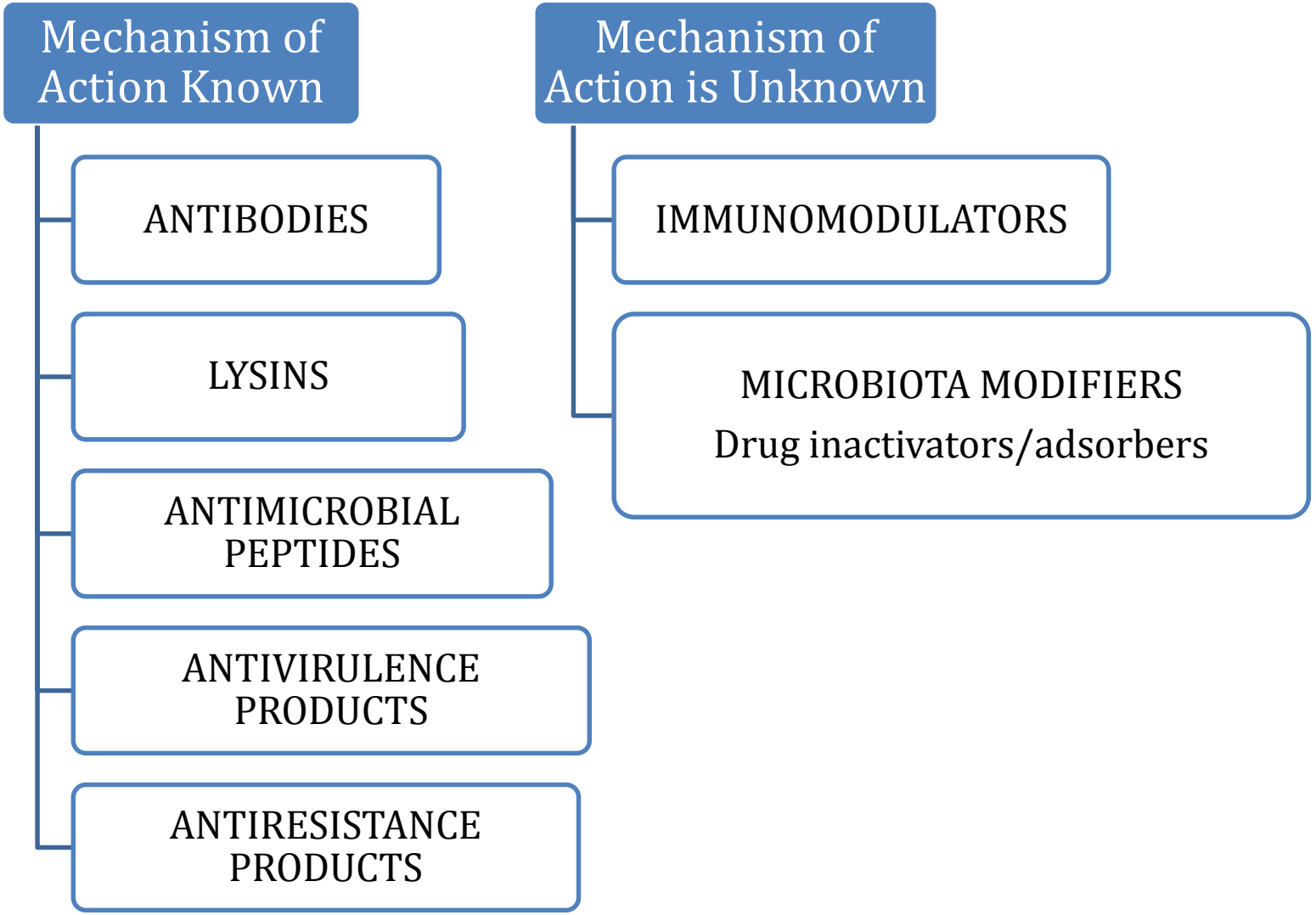
Microbiological Evaluations

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

Mechanism of action



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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