Antibiotic-Resistant Microbe Panel for the Evaluation of New Antimicrobial Agents

Introduction

Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die as a direct result of these infections. The discovery and development of new antibiotics that will be effective against rapidly evolving strains of drug-resistant microorganisms is one of the greatest challenges in drug development today.

To facilitate new antibiotic development, ImQuest BioSciences offers MicroSENS, a full service antimicrobial development platform uniquely combining in vitro, ex vivo and in vivo efficacy and toxicity evaluations. The platform includes preclinical services necessary for the discovery and IND-directed development of antimicrobial agents. With MicroSENS, the sensitivity of test compounds can be rapidly assessed using a diverse panel of microorganisms and candidate compounds can be prioritized to expedite preclinical development.

An essential component of the MicroSens platform is a microbial library of clinically important and genetically defined microorganisms spanning a broad range of resistant gram-negative and gram-positive organisms as well as medically relevant fungal organisms. Custom panels of resistant organisms in the library can be assembled for in vitro screening, animal model validation, or in vivo testing. Panels can be supplemented with relevant microbes for the development of topical microbicides.

For each compound to be tested, these panels are used to evaluate the range and mechanism of antimicrobial activity, determine resistance potential and mechanisms, and examine the efficacy of combinations of antimicrobial agents.

A panel of antibiotic-resistant organisms was selected from the ImQuest microbial library and their sensitivity to control antibiotics was examined. The results are reported herein.

Method and Results

The sensitivity of a representative selection of organisms in our library of antibiotic-resistant organisms to control antibiotics was determined using the CLSI broth micro-dilution method. The minimal inhibitory concentration (MIC) of control antibiotics was then calculated.

The results demonstrated that the test organisms fell into distinct and expected categories of resistant phenotypes, with sensitivity to positive control compounds and resistance to the negative control compounds.
Conclusion

Custom panels of these representative strains and additional antibiotic resistant and quality control organisms can be assembled to define the effectiveness of new compounds for inhibition of resistant organisms.
MicroSENS for Rapid Antibiotic Discovery & Development

The MicroSENS platform includes preclinical services necessary for the discovery and IND-directed development of antimicrobial agents.

Essential elements of the platform include well-established validated assays and analytical tools for in vitro evaluations and an extensive microbial library of clinically important and genetically defined microorganisms spanning a broad range of resistant gram-negative and gram-positive organisms. Test agents can be evaluated for inhibition of pathogenic biofilms and the Minimal Biofilm Inhibitory Concentrations (MBIC) defined.

The MicroSENS platform also includes the evaluation of antimicrobial agents in well-defined animal models, including peritonitis-sepsis and neutropenic thigh models, as well as other more unique and specific animal models.

ImQuest offers customized animal model evaluations depending on the nature of the product and indication to be treated. These models can be performed using antibiotic sensitive or resistant organisms.

ImQuestSUCCESS

Select drug candidates with the highest probability of clinical success

The ImQuestSUCCESS preclinical services platform is used to critically evaluate the potential of a test compound and to assure that its efficacy, toxicity, and pharmaceutical properties are evaluated in a comprehensive and interactive way. Successful completion of platform objectives provides significant confidence in the potential of a test compound to transition to human clinical trials, enhances the robustness of drug development efforts and reduces the risk of expensive clinical development failures by the exclusion of candidates which are likely to fail during advanced preclinical and clinical development at early (and less expensive) time points.
**PrevSENS for the Development of Microbicides to Prevent & Treat Infections**

The PrevSENS platform includes preclinical services necessary for the discovery and IND-directed development of microbicides.

ImQuest BioSciences has the capability to expand the development of antimicrobial compounds to include evaluation of their use as topical agents to prevent or treat sexually transmitted infections (STI) and other skin and wound infections.

Evaluations of topical antimicrobial agents include efficacy and toxicity assays to define lead candidates, range and mechanism of action assays, combination microbicide product development strategies, resistance evaluation, formulation development, and the evaluation of safety and efficacy in ex vivo 3-dimensional tissue models. Inhibition of biofilm formation by test agents can be evaluated with organisms which form biofilms in the vagina or on damaged skin (wounds and burns).

All of our efficacy and toxicity defining assays are performed under conditions that closely mimic the environment in which they are designed to act, e.g., in the presence of vaginal and seminal fluids.

Additional range of action assays can be performed to assess the inhibitory potential of a compound against other viral and bacterial pathogens that might be present during the sexual transmission of HIV and HSV.

Toxic effects of a microbicide to the normal vaginal flora as well as to the cells that comprise the vagina or rectum may reduce the natural capacity of the tissue to prevent infection. For this reason, ImQuest BioSciences evaluates:

- The toxicity of microbicide products in the appropriate cells and tissues.
- The induction of pro-inflammatory cytokine expression in these cells and tissues.

**STI panel for evaluation of activity against:**
- *Chlamydia trachomatis*
- *Trichomonas vaginalis*
- *Neisseria gonorrhoeae*
- Vaginosis Causative Microbes: *Bacteroides fragilis*  
  *Gardnerella vaginalis*  
  *Mobiluncus curtisii*  
  *Candida albicans*

**Toxicity evaluations with:**
- Cervical, vaginal, and rectal cell lines
- Epivaginal tissue
- Normal vaginal flora (including bacteriostatic and bactericidal activity):  
  *Lactobacillus crispatus*  
  *Lactobacillus jensenii*  
  *Lactobacillus acidophilus*