“...The evolution of cell culture”
Antibiotic Resistance

- Emerging antibiotic resistance is a major health concern.
- 2 million people in the U.S. infected with antibiotic resistant bacteria last year
- 23,000 people died as a result of these infections, many more die from complications
- Most deaths related to antibiotic resistance occur in hospitals and nursing homes.
Lack of new antibiotics

• Only 2 systemic antibiotic agents approved since 2008
• 16 approved between 1983 and 1987
• 3 reasons:
  – **Scientific:** Easy to discover antibiotics have already been found
  – **Economic:** Antibiotics represent a poor return on investment and new antibiotics reserved for difficult cases
  – **Regulatory:** FDA approval process increasingly complex and expensive.
• Lowest concentration of a drug that prevents a bacterial inoculum from growing to visibly detectable levels
• Time a drug concentration remains above the MIC
• Ratio of maximal drug concentration to MIC
• Ratio of the area under the concentration time curve to MIC

**MIC: Minimum Inhibitory Concentration**

**Determination of MIC (here: broth dilution test)**

- Organism grown to standard density in broth
- Tubes with increasing drug concentrations inoculated with standard number of organisms
- No visible growth: MIC = 8 μg/ml
- No growth when plated MBC = 16 μg/ml

**Definitions:**
- **MIC:** The minimal concentration of a drug that inhibits the growth of bacteria
- **MBC:** The minimal concentration of a drug that kills the bacteria

**FiberCell Systems**

A better way to grow cells
MIC tells us nothing about:

• Bacteriostatic or bactericidal
• Time or dosage dependent
• Rate of Bacterial killing
• Post-antibiotic effect
• Dosing profiles that prevent or facilitate resistance
Antibiotic efficacy is tied to both concentration and time.
In vitro Testing Methods

• Broth dilution test
• Antimicrobial gradient test
• Disc diffusion test
• E-test
Assays in which both time and concentration are variable:

- Static kill assay
- Mouse thigh infection model
- Hollow fiber infection model
Static kill assay

- Open system, not bio safe
- Bacteria numbers change over time
- Large volume requires large amount of drug and diluent
- Rapid changes in drug concentration not possible, cannot model short half-lifes
Mouse Thigh Infection Model

- PK/PD may not mimic human values
- Cannot sample over time
- Hard to do large numbers of bacteria to reveal resistance
- Many infections cannot be modeled in mouse
Hollow Fiber Infection Model
Hollow Fiber Cross-Section

- **Nutrients In**
- **Drug In**
- **Drug Out**
- **Waste Out**

- **Bacteria or Cells Retained**
- **Hollow Fiber Filter Wall**
- **Extracapillary Space (ECS) Containing Secreted Protein**

*FiberCell Systems - A Better Way to Grow Cells*
Hollow Fiber Cartridge

- Harvest Port(s)
- Capillary Cartridge
- Oxygenator
- Pump
- Media and Growth Factors

FiberCell Systems
A Better Way to Grow Cells
Advantages of the Hollow Fiber Infection Model

• Closed, bio-safe system
• Sampling over time
• Large number of organism can be tested, revealing resistance
• Precisely simulates human PK/PD
• Repetitive sampling over time, both drug and organism
• Total kill
• Single use, disposable, consistent
• Two drug models can be tested
• Can model both dosing curve and elimination curve
• Can look at bacteria in different growth phases and in combination with cells. Antiviral PK/PD as well.
Two Drug Model

- Elimination Reservoir
- Duet Pump
- Cartridge
- Central Compartment 100mL
- Drug A+B Infusion
- Pump
- Pump
- Pump
- Pump
- Diluent #1 to CC
- Diluent #2 to SC
- Drug B Infusion
Hollow Fiber Pretest Study Scheme

Collect samples from the Inbound and Bacterial port for Drug analysis

Inbound drug port

Bacterial sampling port

Collect samples from the Bacterial port for drug analysis

Outbound drug port

Dose system to get a peak of 0.5μg/ml in 1hr. Hold concentration for 1hr. Steady drop mimicking either human or mouse PK

HFS Pretest study → Run drug alone to determine drug compatibility with the system
This drug showed good compatibility with both cartridges.

Not significant enough to consider incompatibility

This drug is not a good candidate for HFS use
Regulatory position

- EMA endorsement for TB
- FDA expected to follow suit
- Cartridges manufactured under ISO-14644-1 class 8
The hollow fiber infection model is a complementary and additional tool for drug development, to be implemented at the earliest stages

• Optimal dose selection and route of administration
• Optimal dosing schedule
• Possible combination therapies
• Defines emerging resistance
• Defines total kill
• Post-approval drug regimen optimization
• Can support trial design for Phase I, II, III and IV clinical trials
Thank you!