Improving Pipeline for the Development of Influenza Antivirals

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BARDA
BARDA Influenza Antiviral Program Strategy Overview

**National Strategy**
- Stockpile
  - 81M Treatment Courses

**Issues**
- Resistance
- SNS/State Stockpiles
- Gaps for Special Populations
- New Antivirals
- Replenishment Costs

**BARDA Strategy**
- IAWG Draft Policy Recommendations
- Extended Expiration Dating

**Accelerated Development To Fill Gaps**
- Hospitalized Pediatrics
- Prophylaxis
- Resistance
- Efficacy
- Treatment Window

**BioCryst Peramivir**
- Biota Laninamivir

**Novel MOA Antivirals**
- Broad-Spectrum Combination Therapies
Issues for Influenza Antivirals

• Current therapies have narrow treatment window
  – Treatment within 48h of symptom onset for neuraminidase inhibitors
  – Can treatment window be expanded with novel antivirals having different mechanisms of action?

• Constant threat of resistance
  – Value of M-2 blockers minimized by resistance
  – Heavy reliance on neuraminidase inhibitors
  – Few combination therapies unavailable

• Limited options in U.S. for special populations
  – No IV formulations approved for patients on ventilators
  – No drugs approved for severely ill, hospitalized patients
  – Limited treatment options for pediatric patients
BARDA Influenza Antiviral Program
Advanced Development Strategy

2005 National Strategy for Pandemic Influenza
• Accelerate development, evaluation, approval and U.S.-based production of new influenza antiviral drugs

Treatment Gap Issues
• Special populations (pediatrics, severely ill hospitalized)

Existing BARDA Advanced Development Projects
• Fill critical unmet medical needs by expanding the utility of neuraminidase inhibitors

• Peramivir
  • $235M contract with BioCryst awarded in 2007
  • Development of IV peramivir in hospitalized patients
  • EUA designated by FDA during 2009 pandemic
    • First unapproved drug authorized for use under an EUA
  • Worldwide clinical program for licensure in U.S.

• Laninamivir
  • $231M contract with Biota awarded in 2011
  • Development of inhaled laninamivir in outpatient setting
  • Single-dose treatment course
Novel Influenza Antiviral Targets in Clinical Development

- **Licensed Drugs**
  - Adamantanes
  - Neuraminidase Inhibitors

- **Other Viral Targets in Clinical Development**
  - Fusion
  - Polymerase
  - Anti-sense
  - ADCC Mab

- **Host Targets in Clinical Development**
  - Inhibit host genes essential for virus life cycle
  - Immunomodulators
    - Up-regulate innate immune response
    - Down-regulate cytokine storm
Host Genes Essential to Virus Life Cycle

  — RNAi screens to identify host pathways involved in influenza virus replication
  — Identified 50 “druggable” genes from 7 functional categories
    • Ribosome
    • COPI vesicle
    • Proton-transporting V-type
    • ATPase complex
    • Spliceosome
    • Nuclear pore/envelope
    • Kinase/signaling

  — Review of cellular targets with drugs that inhibit influenza replication
  — Identified 57 drugs against 36 cellular targets
    • Phase I studies available for 15 of the drugs
### 2012 Influenza Antiviral Landscape

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<tr>
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<th>Pre Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
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**Classifications:**
- **Other**
- **Inhaled**
- **IV**
- **Oral**
2005 National Strategy for Pandemic Influenza

- Accelerate development, evaluation, approval and U.S.-based production of new influenza antiviral drugs

**Treatment Gap Issues**

- Resistance to current therapies
- Limited options for combination therapy
- Limited efficacy and treatment window

**Future Advanced Development Projects**

- Focus on new influenza therapeutics with novel mechanism of action
  - No issue of cross-resistance with current influenza antivirals
  - Potential for combination therapy to improve efficacy and reduce risk of resistance
  - First award to NexBio in Sept 2012
- Focus on novel influenza therapeutics with the potential for broad spectrum activity
  - Target viral functions commonly utilized by many viruses
  - Target host functions that modulate viral infections
    - Specific host function needed for viral replication (NexBio)
    - Immunomodulatory agents
Current Broad Agency Announcement (BAA)  
Area of Interest #4: Influenza Therapeutics

• Smaller, Targeted Contracts for Advanced Development  
  — IND for Influenza indication  
  — Phase I trial completed

• Antiviral Therapeutics for Treatment of Influenza Infection  
  — Therapeutics with novel mechanism of action  
  — Development of combination therapeutics  
  — Alternative formulations for special populations  
  — Identification and validation of surrogate endpoints

• Multi-Purpose, Broad-Spectrum Antiviral Therapeutics for Treatment of Influenza Virus Infection  
  — Viral targets with broad-spectrum potential  
  — Host targets that reduce viral replication and ameliorate symptoms  
  — Combination therapies with an influenza antiviral and a host modulating therapeutic
Questions?