Advancing the Development Pipeline for the Treatment of Influenza

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Influenza Division
BARDA
Roadmap

- What is our goal?
- Where have we been?
- Where are we going?
- Why now?
- What strategies we are pursuing to achieve the goal?
BARDA Influenza Antiviral Program

Program Goal
“Reduce morbidity and mortality in all patient populations during an influenza pandemic by supporting advanced development, evaluation, and approval of new influenza antiviral drugs”

• Mission established in the 2005 National Strategy for Pandemic Influenza, HHS Pandemic Influenza Plan and the 2006 Implementation Plan for the National Strategy for Pandemic Influenza

• Initial stockpiling goal and advanced development projects
  • Stockpile total of 81M treatment courses of influenza antiviral drugs
  • Advanced development of new antiviral drugs

• New BARDA advanced development projects are focused on developing drugs to address critical unmet needs in treating severely ill, hospitalized patients and in pediatric populations
  • Novel mechanisms of action
  • Combination therapy

Our total reliance on monotherapy with NAI’s has placed us at risk of no treatment options to address a potential NAI-resistant pandemic
BARDA Influenza Therapeutics Program Line-Up

- Two large, full development programs for neuraminidase inhibitors
  - BioCryst—treatment of severely ill, hospitalized patients
    - During 2009 pandemic, IV peramivir received the 1st EUA for an unapproved drug
  - Biota—long acting, single dose treatment
- Two smaller, targeted development programs for compounds with novel mechanisms of action
  - Ansun—recombinant sialidase prevents viral attachment to cells
  - Romark—Broad spectrum antiviral targeting host pathways

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<th>FY07</th>
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- NDA Filing

Challenges and Gaps

• Expecting a single drug or class of drugs to treat all stages of influenza infection and all populations might be a stretch
• Historically driven by a limited pipeline
• Leaves gaps in our preparedness:
  ─ Severely ill, hospitalized influenza patients
  ─ More effective treatment options, suitable for all populations including pediatrics
### Influenza Antiviral Landscape in 2006

<table>
<thead>
<tr>
<th>Class</th>
<th>Pre Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
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<td><strong>M2-Blockers</strong></td>
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<td><strong>NA Inhibitors</strong></td>
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<td>Other Viral Targets</td>
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<td>Host Targets</td>
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#### M2-Blockers
- Rimantadine
- Anamantadine

#### NA Inhibitors
- Oseltamivir (Tamiflu)
- Zanamivir (Relenza)
- T-705 (Pirin)

**Other Viral Targets**
- T-705 (Pirin)

**Host Targets**
- Oral
- IM
- Inhaled
- IV

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Please cite this paper as: Wathen et al. (2012) Antivirals in seasonal and pandemic influenza—future perspectives. Influenza and Other Respiratory Viruses 7(Suppl. 1), 76–80.
Influenza Antiviral Landscape 2014

**M-2 Blockers**

**NA Inhibitors**
- TailMed Biologics: Tamiphosphor

**Other Viral Targets**
- Virazole (ribavirin)
- Cap Snatch/Endonuclease
- FluCide™
- Flufirvitide-3
- AVI-7100
- TCAD Combo
- VX-787
- T-705 (Pol in)

**Antibodies**
- iBio: Anti-NA
- 2D1 mAb-HA
- FI6V3 mAb-HA Grp1+2
- CT-P27 mAb-HA Grp1+2
- Anti-Flu A mAb-HA Grp1+2
- Anti-HA
- Equine pAb (H5N1)
- VISTERRA: VIS410 mAb-HA Grp1+2
- CR6261 mAb-HA Grp1
- CR8020 mAb-HA Grp2
- Anti Influenza IVIG

**Inhibitors**
- Zanamivir
- Tamiflu
- Relenza
- RapiActa
- Peramivir
- Hyperimmune IVIG
- University of Hong Kong
- CR9114 mAb-HA Grp1+2
- A06 MAb-HA
- Anti-NA
- Anti-HA
- Fab’entech
- Equine pAb (H5N1)
- Crucell
- Visterra
- Sea Lane
- ContraFect
- NIH
- CF-404
- Anti Influenza IVIG

**Oral**
- Zanamivir
- Tamiflu
- Relenza
- RapiActa

**Inhaled**
- Peramivir

**IV**
- Zanamivir
- Tamiflu
- Relenza
- RapiActa
### Influenza Antiviral Landscape 2014

<table>
<thead>
<tr>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Market Approved</th>
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#### Host Targets

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<thead>
<tr>
<th>Company/Target</th>
<th>Phase</th>
<th>Formulation</th>
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<tr>
<td>NTHi (pro-imf)</td>
<td>Pur矩阵</td>
<td>Oral</td>
</tr>
<tr>
<td>Homspera (Neurokinin-1)</td>
<td>PUR003</td>
<td>Oral</td>
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<tr>
<td>Surfaxin</td>
<td>Fludase</td>
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</tr>
<tr>
<td>GP1002</td>
<td>Nitazoxanide</td>
<td>Oral</td>
</tr>
<tr>
<td>Eforan (Neurokinin-1)</td>
<td>EV-077</td>
<td>Oral</td>
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<tr>
<td>Archaeon Acetyl-salicylic acid (ASA) NF-κB Inhibitor</td>
<td>Other</td>
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<td>Alferon LDO</td>
<td>Ansun BioPharma</td>
<td>IV</td>
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<tr>
<td>Eritoran TLR4 Antagonist</td>
<td>Other</td>
<td>Oral</td>
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<tr>
<td>Fludase</td>
<td>Ansun BioPharma</td>
<td>IV</td>
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<tr>
<td>CC10 protein</td>
<td>Other</td>
<td>Oral</td>
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Where Are We Going?

• We need new options to address pandemic threats
  – Therapies with a wider treatment window
    • >48h of symptom onset
  – Therapies that have a reduced threat of resistance
    • Novel MOA including host directed therapies
    • Combination therapies
  – Options for special populations
    • Alternative formulations (IV for hospitalized)
    • Approved drugs for **severely ill, hospitalized patients**
    • Treatment options and formulations for pediatric patients
  – Broad spectrum activity for influenza and/or other emerging diseases suitable for community use
Shifting Focus. Why now?

• Emergence of antiviral resistance (adamantanes and NAI)
• Lack of drugs to treat late-stage disease – need a wider treatment window for the severely ill hospitalized population
  “A clear advance would be the ability to treat later in the course of disease.” Arnold Monto
• Discovery and development of broadly neutralizing antibodies

Antiviral Therapy 2010; 15:853-859
Broad Spectrum Neutralizing Monoclonal Antibodies

- Target the HA stalk
  - Highly conserved
  - Novel target
  - Broad spectrum – Group 1 and 2, Influenza B

- Unique properties
  - Extended treatment window
  - Long half life resulting in single dose administration
  - Large binding surface reducing likelihood for resistance
Influenza HA and Stalk mAbs

HA1

Head

Stalk

HA2

mAb

mAb
Strategies to Address Unmet Needs

Critical unmet medical needs:

- Severely ill, hospitalized influenza patients
- More effective treatment options, suitable for all populations

• If the drug is a monoclonal antibody, then:
  - Broad spectrum = one or two mAbs cover all subgroups of Influenza A
  - IV formulation amenable to treatment of the severely ill
  - Expanded treatment window = must be effective more than 48 hours after symptom onset

• If the drug is a small molecule, then:
  - Needs to work better than neuraminidase inhibitors (NAIs)
  - Inhibits all Influenza A strains tested
  - Expanded treatment window beyond 48 hours
  - Suitable for combination therapy with existing NAI
  - Oral and IV formulations
Critical unmet medical needs:

- Severely ill, hospitalized influenza patients
- More effective treatment options, suitable for all populations

• If the drug is a host directed therapy, then:
  - Can have direct antiviral activity
  - Restore immunological homeostasis in an influenza infection
  - Demonstrate improved outcomes in the severely ill, hospitalized population when given alone or in combination with SOC antivirals
  - Expanded treatment window = must be effective more than 48 hours after symptom onset
Partnership Opportunities with BARDA

• Broad Agency Announcement (BAA)
  https://www.medicalcountermeasures.gov/newsroom/2013/now-open-broad-agency-announcements.aspx

• Request for Proposal (RFP) FY2015
  — RFP with funding to make base awards for promising programs
Questions?

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