ANTI-INFECTIVES PROGRAM

Melissa Stundick, PhD October 14, 2015

Resilient People. Healthy Communities. A Nation Prepared.
Partner Companies

- Cempra Pharmaceuticals, Inc.
- Chimerix, Inc.
- Emergent Biosolutions
- GlaxoSmithKline
- The Medicines Company
- Regeneron
- Rempex Pharmaceuticals
- Achaogen
- Tetraphase Pharmaceuticals
- SIGA Technologies
- Elusys Therapeutics, Inc.
- Mapp Biopharmaceutical
- BioCryst Pharmaceuticals, Inc.
- ASPR (Assistant Secretary for Preparedness and Response)
Anti-toxin Program

- **Botulism Anti-toxin**
  - Objective: Develop safe and effective botulism antitoxin to treat botulism intoxication
  - BAT™ approved in March 2013
  - Stockpiling goals achieved

- **Anthrax Anti-toxin**
  - Objective: Develop safe and effective anthrax antitoxins to treat inhalational anthrax
  - Raxi approved Dec 2012
  - AIG approved 2015
  - Anthim BLA submitted Mar 2015
  - Stockpiling preparedness goals achieved
Anti-toxin Program

- Future Focus
  - Sustainment and risk mitigation
  - Complete post marketing commitments

- BAA Area of Interest #2.1:
  - 2.1 Development of peptide or small molecule antitoxins, and other novel compounds, with innovative formulations offering enhanced long-term stability. The candidate must be at TRL-6 (active IND and human safety data).
Smallpox Antiviral Program

- BARDA has a requirement for 1.7M treatment courses of smallpox antiviral for use in individuals presenting symptomatic smallpox

- Two ongoing programs, aligns with IOM recommendation and PHEMCE goal for two antiviral drugs with different mechanisms of action

<table>
<thead>
<tr>
<th>Product</th>
<th>Biothreat Spectrum</th>
<th>Commercial Indications</th>
<th>Class</th>
<th>Development Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-246/TPOXX</td>
<td>Smallpox</td>
<td>None</td>
<td>Novel, viral egress</td>
<td>Phase III</td>
</tr>
<tr>
<td>CMX-001/Brincidofovir</td>
<td>Smallpox</td>
<td>dsDNA virus infections</td>
<td>Nucleoside analog</td>
<td>Phase III</td>
</tr>
</tbody>
</table>
Future Trajectory of the Smallpox Antiviral Program

- Support ongoing programs through FDA approval
- Fulfill stockpiling goals
- Transition focus to sustainment and fulfillment of post marketing commitments
Ebola Therapeutics Landscape

Summer 2014

Discovery

Preclinical Development

Phase I

Phase II

IND

Brincidofovir for CMV/Adno

Convalescent Sera

Tekmira

TKM -100802

DEFYRUS

Mapp Biopharmaceutical

Zmab mAbs

ZMapp mAbs

BIOCRYST PHARMACEUTICALS, INC.

BCX4430

SAREPTA THERAPEUTICS

AVI-7530

CHIMERIX, INC.

Brincidofovir for CMV/Adno

MediVector, Inc

Favipiravir for influenza

ASPR

Assistant Secretary for Preparedness and Response
Ebola Therapeutics Landscape

Current

**IND**

**Phases**
- Discovery
- Preclinical Development
- Phase I
- Phase II

**Phases**
- Discovery
- Preclinical Development
- Phase I
- Phase II

**MAPP Biopharmaceuticals**
- TKM-100802
- Convalescent Sera

**Tekmira**
- AVI-7530
- Zmab mAbs

**Merck**
- Trichoderma platform

**Fraunhofer**
- Pichia platform

**Regeneron**
- REGN3477-70-71
- hZMapp mAbs

**Emergent BioSolutions**
- Trichoderma platform

**Medicago**
- BCX4430

**Genentech**
- Mil-77

**DuPont**
- MediVector, Inc

**BARDA Funded**
- Brincidofovir for CMV/Adno
- Favipiravir for influenza

**Bill & Melinda Gates Foundation**
- BARDA Funded
- MAPP Biopharmaceuticals

**Other Ebola mAbs**
- Other Ebola mAbs

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ZMapp Program

- Mapp Contract: ZMapp™ is currently being manufactured at KBP (Kentucky BioProcessing)
  - Manufacturing in tobacco plants starting in August 2014
  - Three monoclonal antibodies that bind to the Ebola glycoprotein
  - Transitioned from DoD and NIAID discovery and early development
  - Six manufacturing campaigns completed to date
  - Additional six manufacturing campaigns – initiated July 2015
  - Phase 3 efficacy study in West Africa and U.S. under the Common Master Protocol started in Feb. 2015

- Medicago and Fraunhofer producing ZMapp™ monoclonal antibodies using their own tobacco plant expression systems
  - Alternative plants and expression system
  - Evaluate activity of ZMapp-like mAbs vs. ZMapp in animal challenge studies
Ebola mAb Therapeutic Long Term Strategy

- Plant derived antibodies
  - Limited capacity to scale-up
  - Limited number of CMOs
  - No approved products

- CHO cell derived antibodies
  - Enormous capacity to scale-up
  - Many CMOs
  - Many FDA approved products
Regeneron Program

- Regeneron has a platform technology to quickly identify novel, mAbs in a murine system and convert to fully human antibodies
- Regeneron is developing a novel 3 mAb cocktail produced in CHO cells
- BARDA awarded a contract to Regeneron in September 2015 to support manufacturing, assay development, IND enabling studies
- Regeneron mAb cocktail has shown efficacy in NHPs when administered 5 dpi
- Regeneron will collaborate with NIH to evaluate mAb cocktail in Phase 1 studies
Biocryst – BCX4430

- BCX4430 is an adenosine analog with activity against Marburg and Ebola viruses
- BARDA/NIAID collaboration to support product development
- BARDA is supporting manufacturing, in vitro and nonclinical toxicology studies
- NIAID funded Phase 1 multiple ascending dose study ongoing (IM formulation)
- Process improvements, scale up, and tech transfer for both IM and IV formulations in progress
- FDA consultations planned re: animal rule approval pathway
Future Trajectory of the Ebola Therapeutics Program

- **Regulatory Pathway Elucidation**
  - A regulatory pathway remains unclear since the first therapeutic is being evaluated for efficacy in a clinical trial – uncertain if this will be achieved
  - Additional nonclinical work will likely be needed to support FDA approval of products under the Animal Rule

- **Manufacturing Process Improvement**
  - New manufacturing technologies need to be explored. Plant based technologies have proven a costly and time consuming approach to MCM manufacturing

- **Fulfill Stockpiling Requirement**
Antibacterial Program
Objective

To help revitalize the antimicrobial pipeline by forming innovative public-private partnerships with companies engaged in antimicrobial therapy development
Why is BARDA Funding Antibacterial Development?

- To enhance biodefense preparedness
- To address the rising rate of antimicrobial resistance globally
- The pace of antibacterial drug development is/will not keep pace with the rate of resistance development without incentives.
# Antibacterial Portfolio

## BARDA’s BSA Supported Product Pipeline

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Compound</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Achaogen</td>
<td>Plazomicin (ACHN-490)</td>
<td>Next-generation aminoglycoside: Broad Spectrum plague, tularemia and carbapenem resistant Enterobacteriaceae (CRE)</td>
</tr>
<tr>
<td>CUBRC/Tetraphase</td>
<td>Eravacycline (TP-434)</td>
<td>A novel fully synthetic tetracycline: Broad Spectrum plague, tularemia, complicated intra-abdominal and urinary tract infections (cIAI, cUTI)</td>
</tr>
<tr>
<td>Cempra</td>
<td>Solithromycin (CEM-101)</td>
<td>Next-generation fluoroquinolone: Broad Spectrum anthrax, tularemia, gonorrhea and community-acquired bacterial pneumonia (CABP)</td>
</tr>
<tr>
<td>Rempex</td>
<td>Carbavance™ (meropenem/RPX7009)</td>
<td>Carbapenem/β-lactamase Inhibitor: Broad Spectrum CRE, cUTI, hospital-acquired pneumonia /ventilator-associated pneumonia (HAP)/ (VAP), melioidosis, glanders</td>
</tr>
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<td>GSK</td>
<td>A portfolio approach</td>
<td>Broad Spectrum Antibiotic Portfolio A partnership to fund multiple compounds to combat antibiotic resistance at various stages of development</td>
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Disclaimer: The above projects are supported by BARDA’s BSA Program utilizing non-dilutive funding via a contract and/or agreement. The stage of development is approximate as of July 2015 (please refer to the sponsors site for updated information). The table represents the compounds most advanced commercial indication being pursued by the developer.
Key Features of the BARDA-AZ Partnership

- Award date: September 15, 2015
- $50M base; $170M total if all options awarded
- HHS’s 2nd ever use of Other Transaction Authority
- Program support a portfolio of antibacterial candidates, the cornerstone of which is aztreonam-avibactam (ATM-AVI)
- Fulfills requirement in CARB National Action Plan that ASPR/BARDA create at least one additional portfolio partnership with a pharmaceutical or biotechnology company by March 2016 to accelerate development of new antibacterial drugs
- Establishes international collaboration between BARDA and the EU’s Innovative Medicines Initiative (IMI)
  - Both entities will provide support for ATM-AVI pivotal trials
## Funding Priorities

### Drug Class
- **Unprecedented**
  - Novel Target
  - Novel Chemistry
- **Precedented**
  - Reduced AR
- **Nontraditional Therapies**
  - mAbs, phage
- **Infection prevention/interdiction**
  - Vaccines
  - Microbiome approach

### Antibiotic Resistance
- **C. difficile**
- **CRE**
- **N. gonorrhea**
- **Acinetobacter**
- **ESBLs**
- **VRE**
- **Pseudomonas**
- **MRSA**
- **Strep pneumo**
- **VRSA**
- **Streptococcus**

### Biothreat
- **B. pseudomallei**
- **B. mallei**
- **F. tularensis**
- **Y. pestis**
- **B. anthracis**
Future Trajectory

- **Key Tenets**
  
a. Develop novel classes antimicrobial therapies with a focus on those with Gram negative activity
  
b. Continue utilizing innovative public-private partnering mechanisms to stimulate therapeutic pipeline
  
c. Work closely with other Govt agencies and private partners to establish and implement policies/practices to ensure pipeline is sustainable
Future Trajectory

- Near-Term Priorities & Strategic Goals (1 year)
  a. Maintain and expand portfolio of precededented and unprecedented classes of antimicrobial therapies
  b. NDA Submission

- Mid-Term Priorities & Strategic Goals (2-3 years)
  a. NDA approval of BARDA-funded products
  b. Expand focus to include approaches that can interdict/prevent infection upon entry into the health care setting
  c. Expand portfolio to include non-traditional therapies (mAbs, probiotics, host targets, etc.)
Interfacing with BARDA

- [www.phe.gov](http://www.phe.gov)  
  - Program description, information, news, announcements
- [www.medicalcountermeasures.gov](http://www.medicalcountermeasures.gov)  
  - Portal to BARDA  
  - Register, request a meeting  
  - Tech Watch
- [www.fedbizopps.gov](http://www.fedbizopps.gov)  
  - Official announcements and detailed information about all government contract solicitations. Open CBRN BAA:  
    - [BAA-13-100-SOL-00013](http://www.fedbizopps.gov)
  Technical POC for Research Area #2: Anti-Toxins and Ebola Therapeutics  
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  [Chiawei.tsai@hhs.gov](mailto:Chiawei.tsai@hhs.gov)
  Technical POC for Research Area #3: Antimicrobial Drugs:  
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