



United States Department of

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Office of the Assistant Secretary for Preparedness and Response

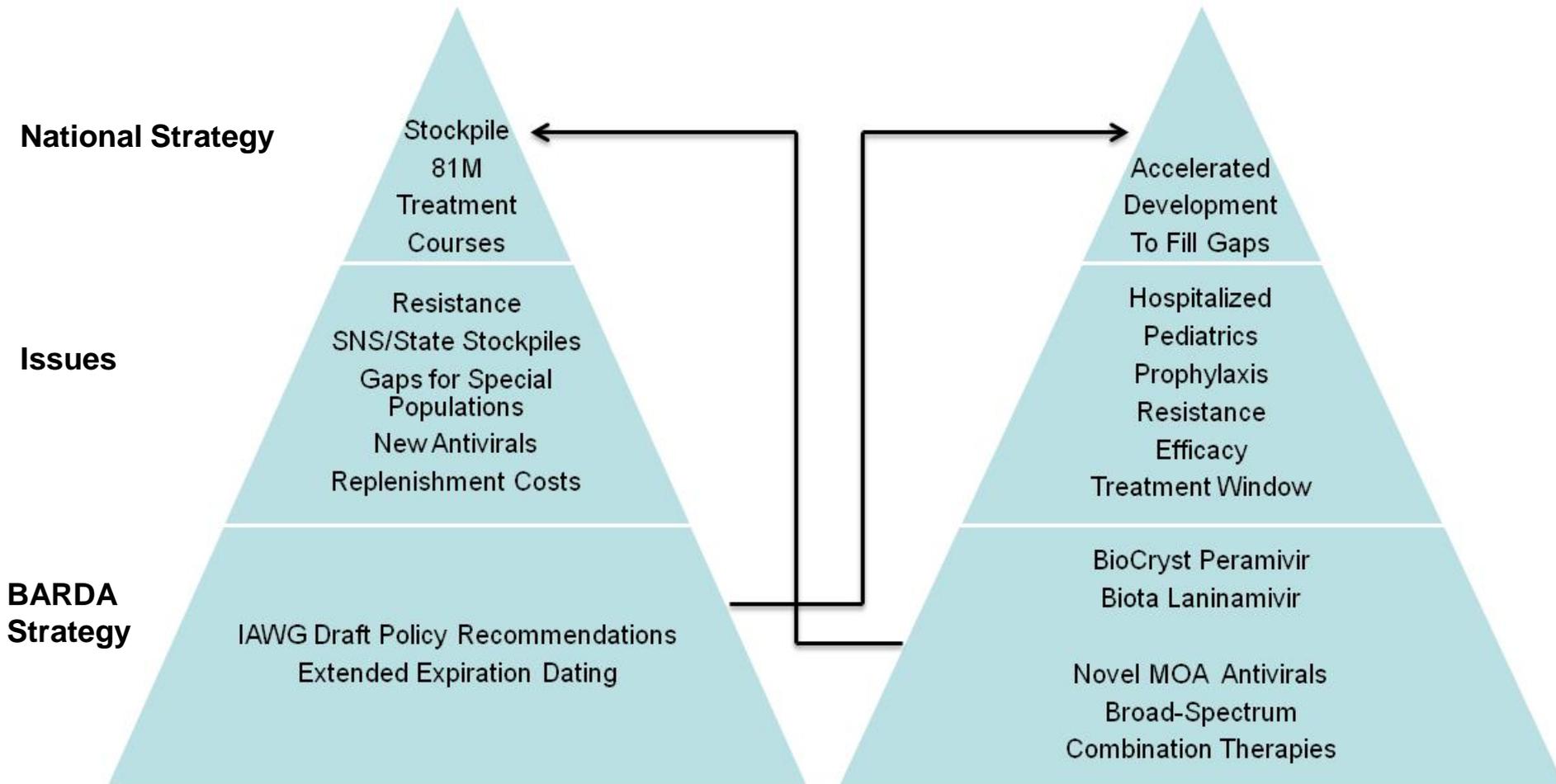


Improving Pipeline for the Development of Influenza Antivirals

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BARDA Influenza Antiviral Program Strategy Overview





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



- ML Shaw (2011) The host interactome of influenza virus presents new potential targets for antiviral drugs. *Rev Med Virol*, DOI:10.1002/rmv.793
 - 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
- KH Muller *et al.* (2012) Emerging cellular targets for influenza antiviral agents. *Trends Pharmacological Sciences*, 33:89-99
 - 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



Class	<u>Pre Clinical</u>			<u>Phase 1</u>	<u>Phase 2</u>	<u>Phase 3</u>	<u>Market Approved</u>	
Adamantananes							Generic Rimantadine	Generic Amantadine
NA Inhibitors	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">TalMed</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Tamiphosphor</div>			<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">★ Biota</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Lanamivir</div>		<div style="background-color: #FFA500; padding: 5px; display: inline-block;">Roche</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Osetamivir</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">GSK</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Zanamivir</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">★ BioCrist</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Peramivir</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">GSK</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Zanamivir</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Daiichi Sankyo</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Inavir</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Roche</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Osetamivir</div>
Other Viral Targets	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">CellTrion CT120</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Fusion Inhibitor</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Mab</div>	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">Sea Lane A06</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Fusion inhibitor</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">HA Mab</div>	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">★ Crucell</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">CR6261/8020</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">HA Mab</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">★ Autoimmune Technologies</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Flufirvitide-3</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Peptide Entry Inhibitor</div>				
	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">Valleant</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Ribavirin</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Pol Inhibitor</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Alnylam</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">RNAi</div>		<div style="background-color: #FFA500; padding: 5px; display: inline-block;">★ AviBioPharma</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">AVI-7100</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">PMO Anti-sense</div>	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">★ Theraclone</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Mab-m2e</div>	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">★ Adamas</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">TCAD Combo</div>	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">★ Toyama</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Favipiravir (T-705)</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Pol Inhibitor</div>	<div style="color: green;">★</div> =NIH Funding <div style="color: red;">★</div> =DoD Funding <div style="color: blue;">★</div> =BARDA Funding
	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Visterra</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Entry Inhibitor</div>	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">Quantum</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Matrix inhibitor</div>		<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Vertex</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">VX-787</div>				
Host Targets	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">★ Kineta</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">RIG-1 Agonist</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Discovery Labs</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Surfaxin</div>	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Immune-Regen</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Neurokinin-1</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Pulmatrix</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">PUR003</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">iCALM</div>	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Evolva</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">EV-077</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">TS Inhibitor</div>			
	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">★ Gemmus</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">GP1002</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">GCCR Agonist</div>	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Pulmotect</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">NTHi</div>	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">Eisai</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Eritoran</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">TLR4 Antagonist</div>	<div style="background-color: #FFA500; padding: 5px; display: inline-block;">★ Functional Genetics</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">Mab host protein</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Archaeon</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">salicylic acid</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Nf-κB Inhibitor</div>	<div style="background-color: #FFFF00; padding: 5px; display: inline-block;">★ NexBio</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Fludase</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Sialidase</div>	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Romark</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Nitazoxanide</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Immuno-modulator</div>	<div style="background-color: #90EE90; padding: 5px; display: inline-block;">Other</div> <div style="background-color: #FFFF00; padding: 5px; display: inline-block;">Inhaled</div> <div style="background-color: #FFA500; padding: 5px; display: inline-block;">IV</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Oral</div>
	<div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">★ Unither</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Virology</div> <div style="background-color: #ADD8E6; padding: 5px; display: inline-block;">Iminosugars</div>			<div style="background-color: #90EE90; padding: 5px; display: inline-block;">★ Clarassance</div> <div style="background-color: #90EE90; padding: 5px; display: inline-block;">CC10 Protein</div> <div style="background-color: #90EE90; padding: 5px; display: inline-block;">Immuno-modulator</div>				



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

- 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



BARDA Influenza Antiviral Program



Questions?