Agricultural Research Service
Biodefense Research

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Vaccines & Diagnostics
for Transboundary Animal Diseases
USDA/DHS Animal Health Countermeasures Pipeline

**Research**
- Discovered candidates

**Early Development**
- Candidate selected for targeted advanced development (TAD)
- DHS TAD Laboratory
- Candidate meets predefined performance metrics

**Full Development**
- Progression to industry and inclusion in USDA National Veterinary Stockpile (NVS) as defined in HSPD-9, paragraph 18a, and National Animal Health Laboratory Network (NAHLN)

**Technical Support**
- Licensing opportunities

**Diagnostics**

**Vaccines**

**Biotherapeutics**

* Milestones

**GAP**

**ANALYSIS**

**ACADEMIA GOVERNMENT INDUSTRY STAKEHOLDERS**

**INDUSTRY APHIS STATES**

**INDUSTRY**

**DISCOVERY**

**ED**

**FD**

**LAUNCH**
Presentation Outline

1. ARS and the Animal Health Biodefense Research Program
2. Setting Priorities
3. New Strategies for Diagnostic and Vaccine Discovery Research
4. Countermeasures Pipeline
5. Conclusion
ARS Mission

“Our mission is to conduct research to develop and transfer solutions to agricultural problems of high national priority . . .”
# ARS National Programs

## Natural Resources & Sustainable Agricultural Systems (~20%)
- Water Quality & Management
- Soil Resource Management
- Air Quality
- Global Change
- Rangeland, Pasture & Forages
- Manure & Byproduct Utilization
- Integrated Agricultural Systems
- Bioenergy and Energy Alternatives

## Crop Production & Protection (~35%)
- Plant, Microbial & Insect Germplasm Conservation & Development
- Plant Biological & Molecular Processes
- Plant Diseases
- Crop Protection & Quarantine
- Crop Production
- Methyl Bromide Alternatives

## Animal Production & Protection (~15%)
- Food Animal Production
- **Animal Health**
- Veterinary and medical entomology
- Aquaculture

## Nutrition, Food Safety & Quality (~30%)
- Human Nutrition
- Food Safety
- New Uses, Quality & Marketability of Plant & Animal Products
Animal Health Strategic Objectives

1. Establish animal disease research programs that integrate basic and applied research into flexible, fluid, and effective research networks that delivers solutions to problems of high national priority
2. Access to specialized high containment facilities to study foreign, emerging, or zoonotic animal diseases
3. Develop integrated animal and microbial genomics research program
4. Establish excellence in animal immunology research
5. Launch biotherapeutic discovery research programs providing alternatives to animal drugs
6. Build technology-driven diagnostic and vaccine discovery research programs
7. Develop core competencies in field epidemiology and predictive biology
8. Establish strategic national and international research collaborations
9. Establish best in class training centers for veterinarians and scientists
10. Develop model technology transfer programs to achieve the full impact of research discoveries
ARS Animal Health Research Locations

- Pullman, WA
- Clay Center, NE
- East Lansing, MI
- Manhattan, KS*
- Ames, IA*
- Plum Island*
- Beltsville, MD
- Athens, GA*
- Fayetteville, AR
- Mississippi State, MS

*Biodefense research
Presentation Outline

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Homeland Security Presidential Directive Nine (HSPD-9) of January 30, 2004, Section 18(a) calls for the development of a “National Veterinary Stockpile (NVS) that shall contain sufficient amounts of animal vaccine, antiviral, or therapeu tic products to appropriately respond to the most damaging animal diseases affecting human health and the economy and that will be capable of deployment within 24 hours of an outbreak.
List of 17 Most Damaging Animal Disease Threats

1. Highly Pathogenic AI (F)
2. Foot-and-Mouth Disease
3. Rift Valley fever (F)
4. Exotic Newcastle Disease
5. Nipah and Hendra virus (F)
6. Classical swine fever
7. African swine fever
8. Bovine spongiform encephalopathy (F)
9. Rinderpest
10. Japanese encephalitis (F)
11. African horse sickness
12. Venezuelan equine (F) encephalitis
13. Contagious bovine pleuropneumonia
14. Ehrlichia ruminantium (Heartwater)
15. Eastern equine encephalitis (F)
16. Coxiella burnetii (F)
17. Akabane virus

F: Potentially fatal to humans
Gold text: FBI pathogens of Concern
Emerging Diseases
(and re-emerging diseases)

**Human**
- HIV/AIDS
- Ebola*
- Hantaan
- Legionaire’s disease
- BSE*
- SARS*
- Dengue
- West Nile*
- Nipah virus*
- Rift Valley Fever*
- Chikungunya virus
- H5N1 AI*
- pandemic H1N1
- H3N2v*

* Zoonoses

**Animal**
- BSE*
- Ebola*
- CWD
- West Nile*
- Foot-and-Mouth Disease
- Classical Swine Fever
- Blue Ear Pig Disease
- Rift Valley Fever*
- Avian Influenza*
- Nipah and Hendra*
- African Swine Fever
- pandemic H1N1**
- Schmallenberg virus
- H3N2v*

** Reverse Zoonosis**
U.S National Veterinary Stockpile Gap Analyses

- Gap analysis of scientific information
- Countermeasures assessment
- Recommendations for research and stockpile

- Rift Valley Fever – Pasteur Institute, France
- Avian Influenza – ARS, Washington D.C, United States
- Foot-and-Mouth Disease – INTA, Argentina
- Exotic Newcastle Disease – SEPRL, Athens, GA, United States
- Nipah virus – AAHL, Australia
- Classical Swine Fever – CSF, Germany
- African Swine Fever – ASF, Spain
Interagency Working Group
Foreign Animal Diseases Threats

Co-Chairs: Dr. Michelle Colby (DHS S&T), Dr. Steven Kappes (USDA ARS)

Membership:
- Department of Agriculture
- Department of Defense
- Department of Health and Human Services
- Department of Homeland Security
- Department of Interior
- Department of State
- Environmental Protection Agency
- National Science Foundation

Representation from the Executive Office of the President
- Office of Science & Technology Policy
- Homeland Security Council
- Office of Management and Budget
- Office of the Vice President
Prioritization activities

- Basic Research
  - Ecology
  - Immunology
  - Pathology
  - Genomics
  - Microbiology
- Veterinary Countermeasures
  - Vaccines
  - Diagnostics
- Depopulation, Disposal and Decontamination
- Modeling
Interagency Working Group
Foreign Animal Diseases Threats

Published 5 year R&D strategy
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Diagnostic Technologies

- Reverse transcription polymerase chain reaction (RT-PCR)
- Real time RT-PCR
- Multiplex RT-PCR
- Isothermal technologies - Loop mediated amplification (LAMP)
- DNA chips (Microarrays)
- Liquid array technologies (Multiplex Luminex assays)
- Lateral-flow devices (Dip stick)
- Enzyme-linked immunosorbent assay (ELISA)
- Solid-phase competition ELISA (SPCE)
- Liquid-phase blocking ELISA (LPBE)
- Enzyme-linked immunoelectrotransfer blot assay (EITB)
- Enzyme immune assay membrane tests
- Rapid microchip based electrophoretic immunoassays
- Allosteric biosensors
- Molecular imprinting techniques on quartz crystal microbalance
New Strategies for Diagnostic Discovery

1. **Surveillance**
   1.1 Tests to detect infected animals

2. **Response**
   2.1 Tests in the early stages of an outbreak
   2.2 Tests for early and sustained response
   2.3 Tests to detect infected animals

3. **Recovery**
   3.1 Tests to demonstrate absence of infection
   3.2 Tests to differentiate infected from vaccinated animals (DIVA tests)
   3.3 Tests to detect carrier animals

4. **Post-outbreak surveillance**
   4.1 Tests to enable confirmation of freedom from disease
Vaccine Technologies

**Attenuated vaccines**

- Systems biology approach
- Reverse genetics, temperature-sensitive mutations, and reassortment
- Viral recombinants and deletion mutants
- Codon de-optimization
- Control of replication fidelity
- MicroRNA insertion
- Replication vectors that contain genes from pathogens
Inactivated vaccines

- Structural biology approach
- DNA plasmids
- Reverse vaccinology
- Antigen identification by transcriptomics and proteomics
- Development of fusion proteins
- Development of new adjuvants (including cytokines)
- Induction of innate immunity

New Strategies for Vaccine Discovery

• Effective, rapid and long-lasting protection with one inoculation
• Prevents transmission
• Allow differentiation of infected from vaccinated animals (DIVA)
• Produce without the need for virulent virus
• Prevent development of carrier state
• Protection against multiple serotypes (Cross-protection)
• Stable antigen – long shelf life
1. ARS and the Animal Health Biodefense Research Program
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Concerns with FMD Vaccines

- Require adaptation and growth of large volumes of wild type virus in cells
- Escape of virus from manufacturing facilities
- Require banking of multiple antigen concentrates
- Some antigens lack stability (low potency/short shelf life)
- Onset of protection 7-14 days
- Short duration of immunity ≤6 months
- Difficult to differentiate vaccinated from infected animals (DIVA) due to presence of NS proteins
- Vaccinated and exposed animals become carriers
Adenovirus-Vectored FMD Vaccine Expressing Empty Viral Capsids

- Contains all protective epitopes present on current inactivated virus vaccine but lacks infectious viral nucleic acid and non-structural protein (NSP)
- Allows to "clearly" distinguish vaccinated from infected animals using 3D and other NSP diagnostic tests
- Can be safely produced in the United States

DHS TAD Program
Licensed by CVB-APHIS
VISION OF GFRA
A coordinated global alliance of scientists producing evidence and innovation that enables the progressive control and eradication of FMD.

MISSION OF GFRA
To establish and sustain global research partnerships to generate scientific knowledge and discover the tools to successfully prevent, control and eradicate FMD.

PROGRAMS OF GFRA
GFRA aims to expand FMD research collaborations worldwide and maximize the use of resources and expertise to achieve its five strategic goals (see below).

Several research programs are currently active in Europe, North America, South America and South-East Asia. GFRA programs will continue to expand the alliance in these areas and will actively reach out to new areas of the world that have a stake in the progressive control and eradication of FMD.

STRATEGIC GOALS OF GFRA

http://www.ars.usda.gov/GFRA/
**FMD-LL3B3D Product Profile**

- **Safe production**: attenuated in cattle and pigs
- **Easy production**: uses same production system as current FMD vaccines
- **Simplified downstream processing**: no need for NSP removal
- **Non transmissible** from cattle and swine
- **Negative markers**: 2 independent DIVA compatible markers
- **Immunogenic**: same as current inactivated vaccine
- **Cassette construct** allows to rapidly insert capsid-coding region from emerging strains

![Diagram showing the cassette construct and markers]
Presentation Outline

1. ARS Biodefense Research Program
2. Animal Health Countermeasures Pipeline
3. New Strategies for Vaccine and Diagnostic Discovery Research
4. What’s in the ARS Pipeline
5. Conclusion
USDA/DHS Animal Health Countermeasures Pipeline

Research  Early Development  Full Development  Technical Support

ADACEMIA  GOVERNMENT  INDUSTRY  STAKEHOLDERS

GAP  ANALYSIS

DISCOVERY  ED  FD  LAUNCH

Diagnostics

Vaccines

Biotherapeutics

Candidate selected for targeted advanced development (TAD)

DHS TAD Laboratory

Candidate meets predefined performance metrics

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* Milestones

Licensing opportunities

Licensing

Patents

Contract research

Technical transfers

CVB-APHIS License

DHS

**
Thank you!

Global Foot-and Mouth Disease Reasearch Alliance (GFRA)
2008 Executive Committee Meeting
May 20th - 21st 2008