Overview
USAHA – FED
2012

Agricultural Research Service, Plum Island Animal Disease Center
APPROVED NEW CRIS PROJECTS 2012-2017

• Intervention Strategies to Support the Global Control and Eradication of FMD

• Countermeasures to Control Foreign Animal Diseases of Swine: CSF/ASF

• Ecology and pathogenesis of Re-Emerging VSV in North America
Foot and Mouth Disease

- FMD is considered number one threat to American Agriculture and related industries (livestock, crops, farm supply, etc)

- FAO/OIE announced eradication from Americas by 2023 – global strategy key to eradication

- FMD is main barrier to international trade of animal products

- FMD is one of the main threats to global food security

“Countries infected with FMD are more prone to food insecurity as a result of the impact of FMD at household level and through reduced access to local, national and international markets and of animal draught power for agriculture”

OIE/FAO, 2009
Current vaccines
Concerns with FMD Vaccines

- **SAFETY**: Require adaptation and growth of large volumes of wild type virus in cells → possibility of escape of virus from manufacturing facilities

- **EFFICACY**:
  - Narrow antigenic coverage (serotype / subtype)
  - Short duration of immunity < 6 months
  - Vaccinated and exposed animals become carriers
Characteristics of an “Ideal” FMD Vaccine

- Effective, rapid and long-lasting protection with one inoculation
- Prevents viral transmission
- Allow differentiation of infected from vaccinated animals (DIVA)
- Safe: produced without the need for virulent FMDV
- No need for adaptation of field strains to cell culture
- Prevent development of carrier state
- Broad antigenic coverage
- Stable antigen – long shelf life
- Long duration of immunity
Double marker cDNA-derived Killed FMDV Vaccine Platform

**Vaccine seed antigens**
Easy swap of capsid sequences

**Attenuating factor**
Deletion of Leader protein (543 bp)
Safety Data Cattle

<table>
<thead>
<tr>
<th>Bovine #</th>
<th>Virus</th>
<th>Viremia, Maximum Titer, b (DPI) c</th>
<th>Virus in Saliva, Maximum Titer b (DPI) c</th>
<th>Fever d (DPI) e</th>
<th>Maximum Clinical Score/Maximum achievable f (DPI) g</th>
<th>Neutralization Titer maximum (Starting DPI)</th>
<th>Shedding in air. Maximum Titer l (DPI) c</th>
</tr>
</thead>
<tbody>
<tr>
<td>7109</td>
<td>$A_{24}WT$</td>
<td>7.60 (3)</td>
<td>8.90 (3)</td>
<td>Yes (2,3)</td>
<td>5/5 (7)</td>
<td>2.4 (5)</td>
<td>5.57 (5)</td>
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<tr>
<td>7110</td>
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<td>7.31 (4)</td>
<td>10.18 (3)</td>
<td>Yes (2-5)</td>
<td>5/5 (5)</td>
<td>2.4 (6)</td>
<td>ND</td>
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<td>9143</td>
<td>$A_{24}WT3B_{m3D_{m}}$</td>
<td>7.40 (4)</td>
<td>9.03 (5)</td>
<td>Yes (3)</td>
<td>1/5 (5)</td>
<td>3.6</td>
<td>6.29 (6)</td>
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<td>9144</td>
<td>$A_{24}WT3B_{m3D_{m}}$</td>
<td>7.92 (4)</td>
<td>8.85 (5)</td>
<td>Yes (4)</td>
<td>4/5 (7)</td>
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<td>5.45 (7)</td>
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<tr>
<td>9145</td>
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<td>Negative</td>
<td>Negative</td>
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<td>0/5</td>
<td>1.5</td>
<td>ND</td>
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<tr>
<td>9146</td>
<td>$A_{24}LL3B_{m3D_{m}}$</td>
<td>Negative</td>
<td>Negative</td>
<td>No</td>
<td>0/5</td>
<td>2.4</td>
<td>Negative</td>
</tr>
</tbody>
</table>

FMD-LL3B3D is fully attenuated in cattle!
Efficacy Data Cattle
BEI-inactivated Vaccine formulated with montadine ISA 260 adjuvant (Sepic-WOW) 21 dpv challenge with FMDV-A24

Commercial Tetravalent FMDV Vaccine
1xBEI- Vx

N=4

FMD-LL3D FMDV Vaccine
1x BEI Marker virus

N=4

FMD-LL3B3D FMDV Vaccine
1x BEI Marker virus

N=4

Naïve unvaccinated controls

No clinical disease (0/4)*
No clinical disease (0/4)*
No clinical disease (0/4)*

100 % clinical disease (4/4)

Inactivated vaccines prepared with FMD-LL3D and FMD-LL3B3D induced complete protection against challenge!
Characteristics of an “Ideal” FMD Vaccine

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  - Broad antigenic coverage
  - Stable antigen – long shelf life
  - Long duration of immunity
Novel Ad5-FMD Vaccine

- A novel FMD vaccine was developed by ARS scientists under the leadership of Dr. Marvin Grubman

- This vaccine utilizes a defective human adenovirus vector to deliver genes coding for FMDV structural proteins

**Human Defective Adenovirus 5 vector**
- Lacks necessary proteins for growth
- Delivers and expresses transgenes in target cells
First Licensed Molecular FMD Vaccine

- **N=6**
  - 1° Vx
  - 100% protection (10/10)

- **N=4**
  - 2° Vx
  - 100% protection (10/10)

- **N=6**
  - 1° Naive
  - 100% clinical disease (10/10)

- **N=4**
  - 2° Naive

**DHS- TAD Group**
Characteristics of an “Ideal” FMD Vaccine

- Effective, rapid and long-lasting protection with one inoculation
- Prevents viral transmission
- Allow differentiation of infected from vaccinated animals (DIVA)
- Safe: produced without FMDV !!
- No need for adaptation of field strains to cell culture
  - Prevent development of carrier state
  - Broad antigenic coverage
  - Stable antigen – long shelf life
  - Long duration of immunity
Implications

• What does this vaccines add for US preparedness?
  – Possibility of domestic production
  – Rapid response to new strains
  – Opened regulatory path to other molecular vaccines

• Implications to the hemisphere?
  – Potential application in final stages of eradication?
APPROVED NEW CRIS PROJECTS 2012-2017

- Intervention Strategies to Support the Global Control and Eradication of FMD

- Countermeasures to Control Foreign Animal Diseases of Swine: CSF/ASF

- Ecology and pathogenesis of Re-Emerging VSV in North America
Beginning of 2007 in R. of Georgia and has since spread to the neighboring countries of Armenia, Azerbaijan, Ukraine and Russia
Develop intervention strategies to control ASF virus by identifying virus-host determinants of virulence and transmission and by developing technologies to enable the development of ASF vaccines that are efficacious against the most prevalent ASF strains.

- Development and standardization of a challenge model to assess ASFV experimental immunogens

- Comparative studies of early pathogenesis events in swine during infection with highly virulent and attenuated ASFV strains using a natural route of infection.

- Identification of immune mechanisms mediating protection induced by experimental live attenuated vaccine strains

- Functional Genomics and development of ASFV experimental vaccines
Hypothesis: Oronasal (simulated natural) inoculation of pigs will allow elucidation of critical virus-host interactions which may be targeted by novel countermeasures.

Standardized intra-oral deposition of ASFV under sedation.

Dr. Jonathan Arzt
Functional genomics

- Structural proteins: p30, p72, p54
- Immune response modulation: 5EL (IkB), 8CR (lectin), 8DR (CD2)
- Prevention of apoptotic cell death: 5HL (Bcl2), 4CL (iap)

Host range and virulence associated genes

- NL, UK, 9GL, TK
- Multigene family (MGF) 360 genes
- Multigene family (MGF) 530 genes

Dr. Manuel Borca
Genetic engineering of ASFV

INFECTION

ASFV

PCR

Amplify left flank
Amplify right flank

INSERT REPORTER GENE

Transfer Vector (TV)

RECOMBINATION

Macrophages

TV
△9GL confers strain-specific protection

<table>
<thead>
<tr>
<th>Immunization</th>
<th>MAL△9GL</th>
<th>TEN△9GL</th>
<th>Pr4△9GL</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAL (Malawi’83)</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
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<tr>
<td>TEN (Tengani’54)</td>
<td>NO</td>
<td>YES</td>
<td>NO</td>
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<tr>
<td>RSA1 (Pr4’96)</td>
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<td>NO</td>
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<tr>
<td>RSA2 (Pr5’96)</td>
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<tr>
<td>RSA3 (CR1’96)</td>
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<tr>
<td>RSA4 (CR3’96)</td>
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<td>YES</td>
</tr>
<tr>
<td>RSA5 (O1’96)</td>
<td></td>
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<td>YES</td>
</tr>
</tbody>
</table>

ASFV challenge (1,000-10,000 LD$_{100}$)

Protection in pig
Production of recombinant Georgia ASFV ΔCD-2 like

ΔASFV genes
9GL
NL
UK
MGF
CD-2 like
What next

- Comparative studies of early pathogenesis events in swine during infection with highly virulent and attenuated ASFV strains using a natural route of infection.
- Determine protection induced by experimental live attenuated vaccine strains.
- Identification of immune mechanisms mediating protection induced by experimental live attenuated vaccine strains.
- Expression of multiple ASFV immunogens in replicating viral vectors (e.g. vaccinia) to assess immune response and protection from challenge.
Strategic partnerships

- **Government**: DHS, USDA/APHIS, EPA, DOD, DOS, DOE
- **Stakeholder**: National Pork Board (>2 M in last 4 years)
- **Academia**: UConn, Kansas State, U.Georgia, Stonybrook, U. Wisconsin, U. Vermont, Texas A&M
- **Industry**: Pfizer, Merial, Intervet, GenVec
GLOBAL PARTNERSHIPS

“To establish and sustain global research partnerships to generate scientific knowledge and discover the tools to successfully prevent and control FADs”

Countries with current research collaborations

- India  Australia
- Spain  Pakistan
- Vietnam  South Africa
- UK  Argentina
- Kenya  Cameroon
- Russia  R. Georgia
- S.Korea  Japan
- Mexico  Uganda
- Israel  Denmark
African Swine Fever Research Alliance

- Kick-off meeting at Plum Island Animal Disease Center
- April – or May 2013
- More to come