New Vaccine And Countermeasures Research

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Global Foot-and-Mouth Disease Research Alliance

ARS USDA

OUTLINE

- FMDV molecular platform for safe vaccine production
- Adenovirus vector as FMD vaccine platform
- Research collaborations and opportunities under GFRA

The problem: Foot-and mouth disease (FMD) has been described as THE MOST contagious disease of animals

- FMD is the major animal disease preventing world trade of animals and animal products
- Mortality is low but morbidity is high
- High mortality associated with some control methods

Wrong for farmers to pay for Pirbright foot and mouth leak

By Anna Burdett Farming and rural affairs editor

Last updated 14:45, Friday, 24 October 2008

A Carlisle farmer who is among a group suing Defra secretary Hilary Benn over last year's foot and mouth outbreak says it is wrong for farmers to pay for the Pirbright leak.

Colin Hebson

Colin Hebson, 42, of Chapel Farm, Cotehill, is one of 14 farmers claiming £1.5 million in damages from the Institute for Animal Health (IAH), operators of the Pirbright research facility in Surrey.

The High Court claim also names Defra Secretary of State Hilary Benn as licensor and regulator of the facility.

Mr Hebson said: "I'm doing this because I think what happened was wrong.

Methods to Control FMD Outbreaks

- In FMD-free countries regaining FMDV-free status and return to trade is the #1 priority
  - Stop animal and product movement
  - Slaughter infected and susceptible in-contact animals
  - Disinfect contaminated areas
  - Demonstrate freedom of FMDV – no vaccination
  - Risk: Virus might spread out of control areas

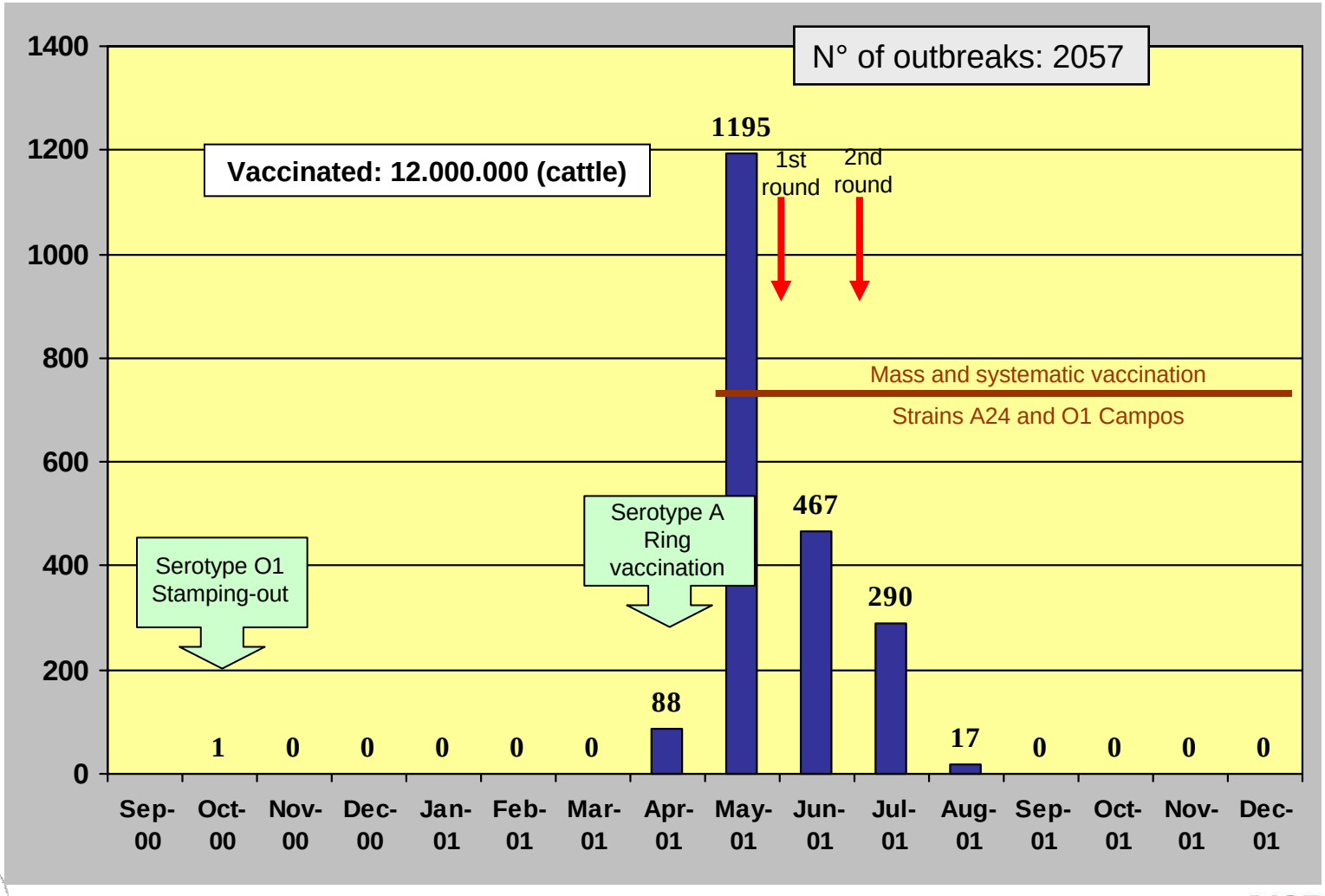
OR

  - Vaccination with an inactivated whole virus antigen
  - No slaughter – free with vaccination – limited trade
  - Slaughter of vaccinated animals – free status ➔ trade

- *Inactivated vaccine was a critical component* of the strategy that resulted in elimination of FMD from Western Europe in 1980's and in parts of South America in 1990s

FMD Control With Inactivated Vaccine

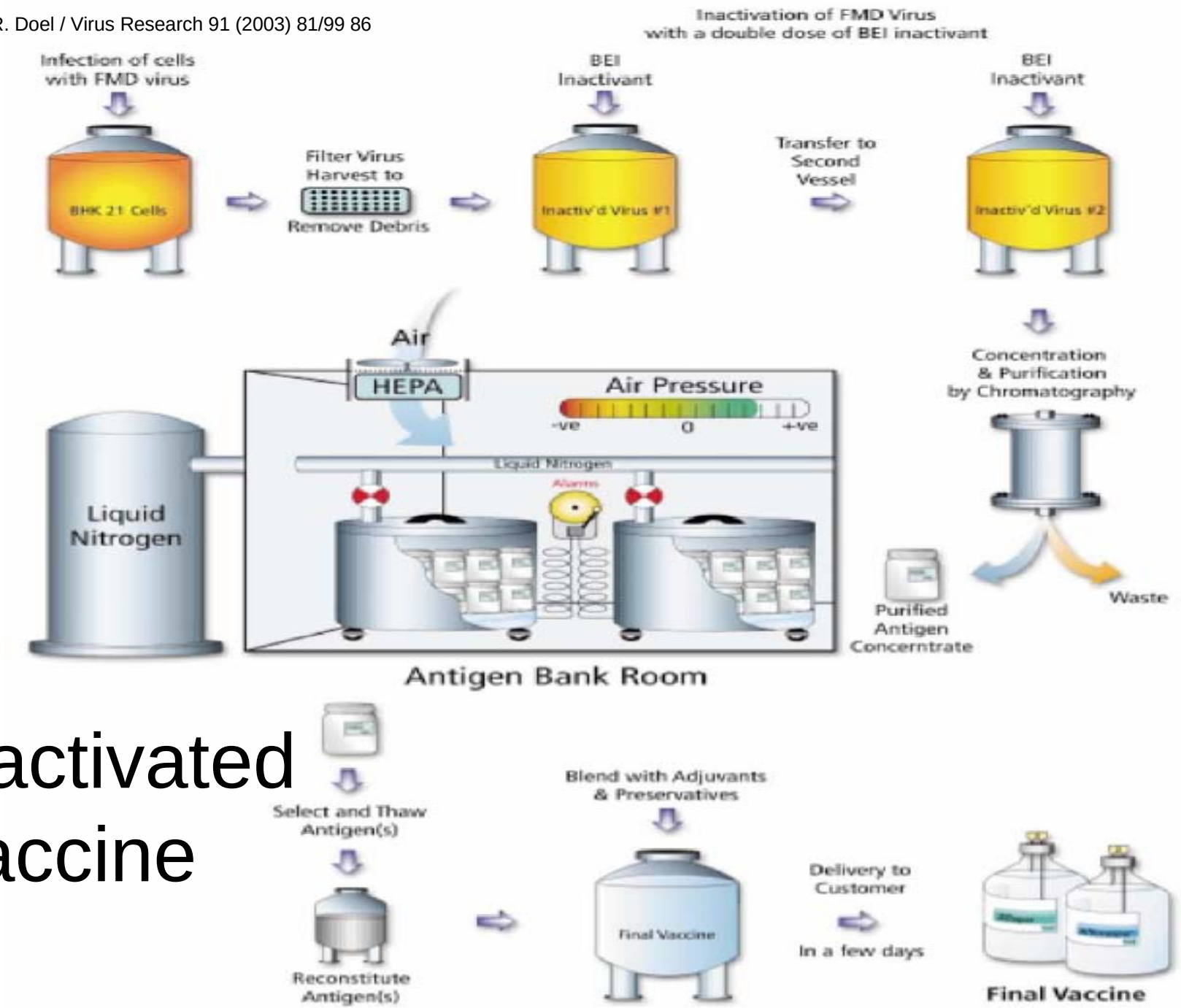
Epidemic - Uruguay 2000-2001



Source: Sergio J. DUFFY DVM, MSc, PhD, Argentina

T.R. Doel / Virus Research 91 (2003) 81/99 86

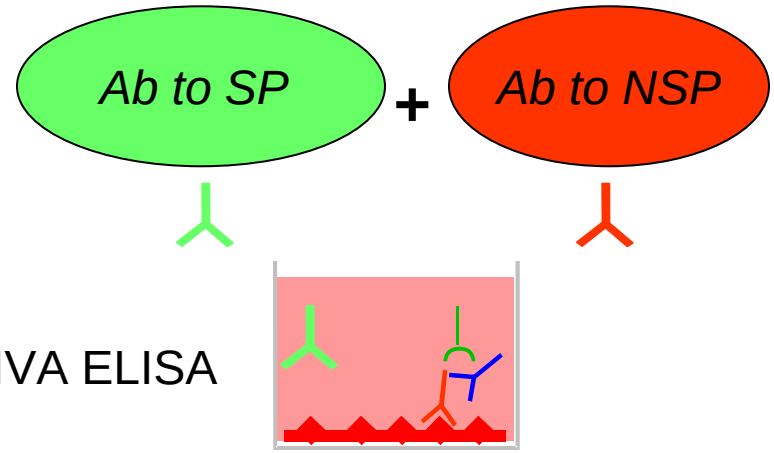
Inactivated Vaccine



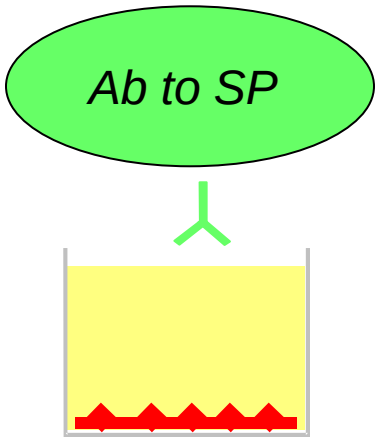
Antibody response to FMDV

- Virus infection or vaccination

- Negative marker vaccine



DIVA ELISA



T.Beckham

Concerns with Current FMD Vaccines in *Disease-Free* Countries

- 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 due to presence of NS proteins
- Vaccinated and exposed animals become carriers

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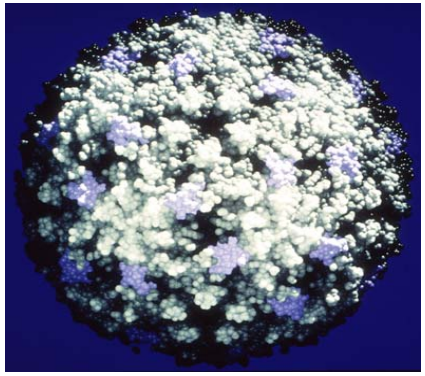
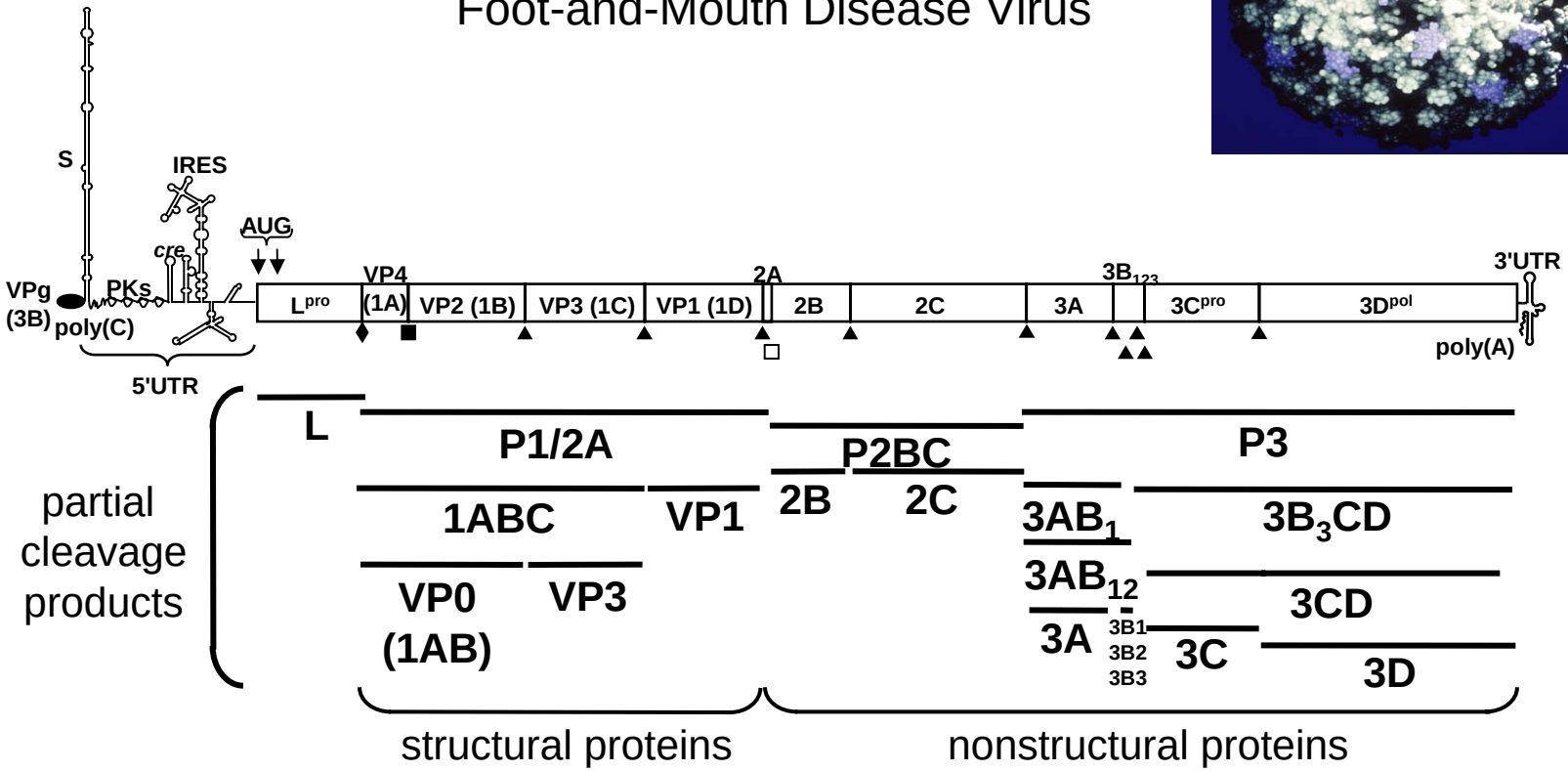
Characteristics of an “Ideal” FMD Vaccine

- Effective, rapid and long-lasting protection with one inoculation
- Prevents viral transmission
- Allow differentiation of infected from vaccinated animals (DIVA)
- Produced without the need for infectious FMDV
- Prevent development of carrier state
- Protection against multiple serotypes
- Stable antigen – long shelf life

Rationally Designed FMD Vaccines



Foot-and-Mouth Disease Virus



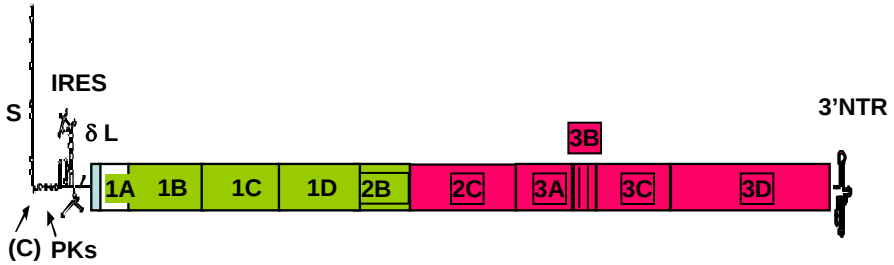
- Identification of genomic regions determining virulence
- Identification of antigenic epitopes associated to infection
- Engineering FMDV to attenuate and remove antigenic sites

Protease Cleavage Sites

L^{pro} ◆	unknown ■
2A □	$3C^{pro}$ ▲

Genetically Engineered FMDV For Safe Inactivated Vaccine Production

- Safe production: attenuated in cattle and pigs
- Non transmissible from cattle and swine
- Negative markers: DIVA compatible
- Immunogenic: same or better than current inactivated vaccine
- Cassette construct allows to rapidly insert capsid-coding region from emerging strains



E. Rieder et al.

FMD Vaccine Product Profiles : Current Inactivated vs. Molecular Inactivated Vaccine

PRODUCT PROFILE	CURRENT INACTIVATED	Molec. Inactive VACCINE
Prevents viral transmission	✓	✓
Early onset of immunity (7 days)	✓	✓
Marked vaccine (DIVA capable)	No	✓
Long Duration of immunity (>1 yr)	No	No
Prevents carrier state	No	No
Domestic production (USA)	No	possible ✓
Long-term stability formulated product	No	No
Readily deployable (ready to use)	No	No
Compatible with “vaccinate to live” strategy	No	✓
Provides cross-serotype protection	No	No

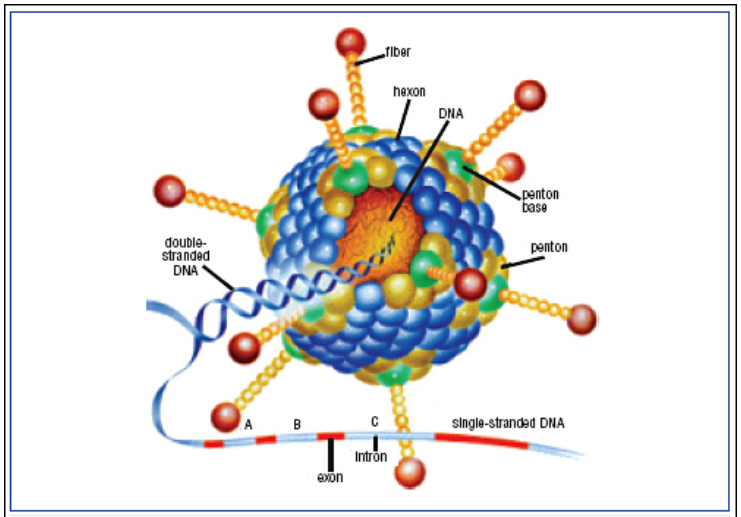
Subunit vaccines

- FMDV structural proteins contain protective epitopes described to date
- First attempt FMD VP1 –E. coli – not successful
- DNA and peptide vaccines, require several immunization and are not fully protective
- Full protection requires conformational antigens

Novel Subunit Vaccines

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

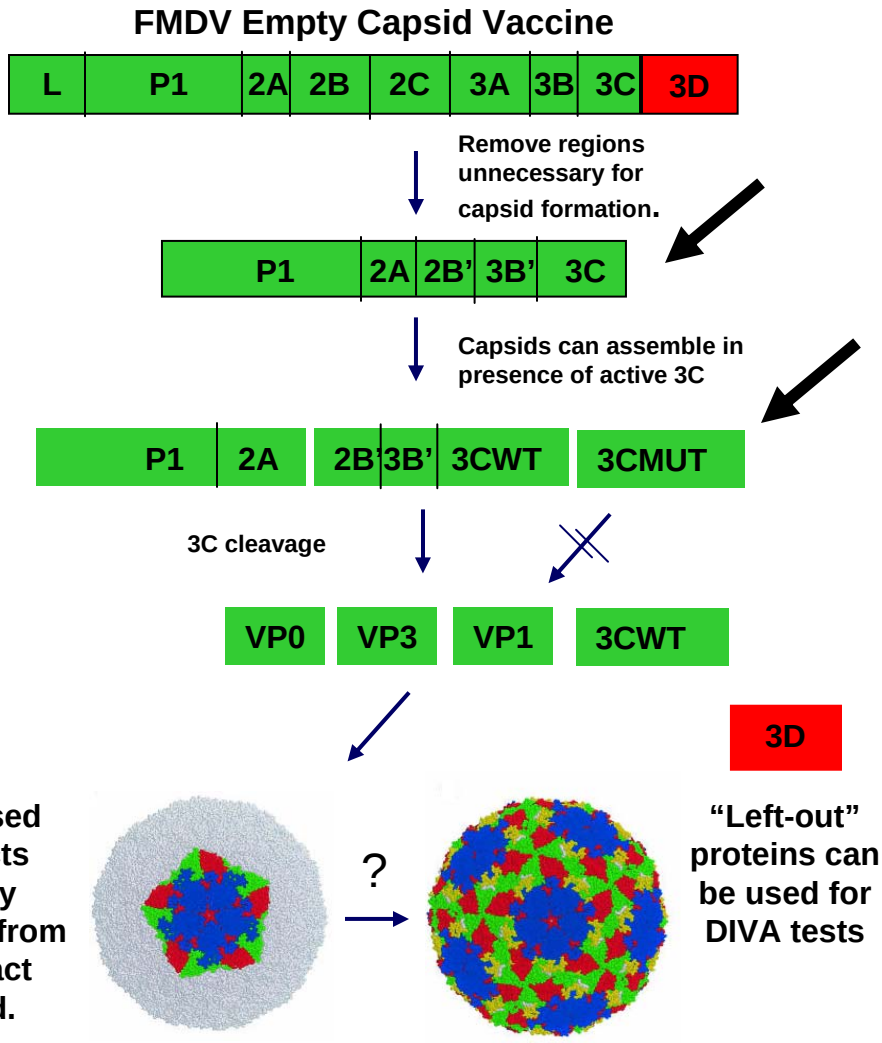
- This vaccine utilizes a defective human adenovirus vector to deliver genes coding for FMDV structural proteins



Human Defective Adenovirus 5 vector
- Lacks necessary proteins for growth
- Delivers and expresses transgenes in target cells

Multi-epitope Immunogen: Empty Viral Capsids (EVC)

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



Dr. M. Grubman

One Dose of Ad5-FMD Vaccine Protects Swine in Seven Days

Vaccine	Challenge	Mean Neut Ab (0 dpc)	Viremia	Protection
Mock vaccine	14dpv	<8	Yes	Severe disease
Ad5-A24	7dpv	36	No	No disease
Ad5-A24	14dpv	280	No	No disease

Swine vaccinated with a single dose of Ad5-A24 are protected from challenge 7 days later.

FMD Vaccine Product Profiles: Current Inactivated vs. New Generation Molecular Vaccine

PRODUCT PROFILE	CURRENT INACTIVATED	Ad5-FMD
Prevents viral transmission	✓	✓
Early onset of immunity	✓	✓
Marked vaccine (DIVA capable)	+/-	✓
Domestic production (USA)	No	✓
Long-term stability formulated product	No	✓
Readily deployable (ready to use)	No	✓
Compatible with “vaccinate to live” strategy	No	✓
Provides cross-serotype protection	No	No

R&D Challenges Remaining For FMD Vaccines

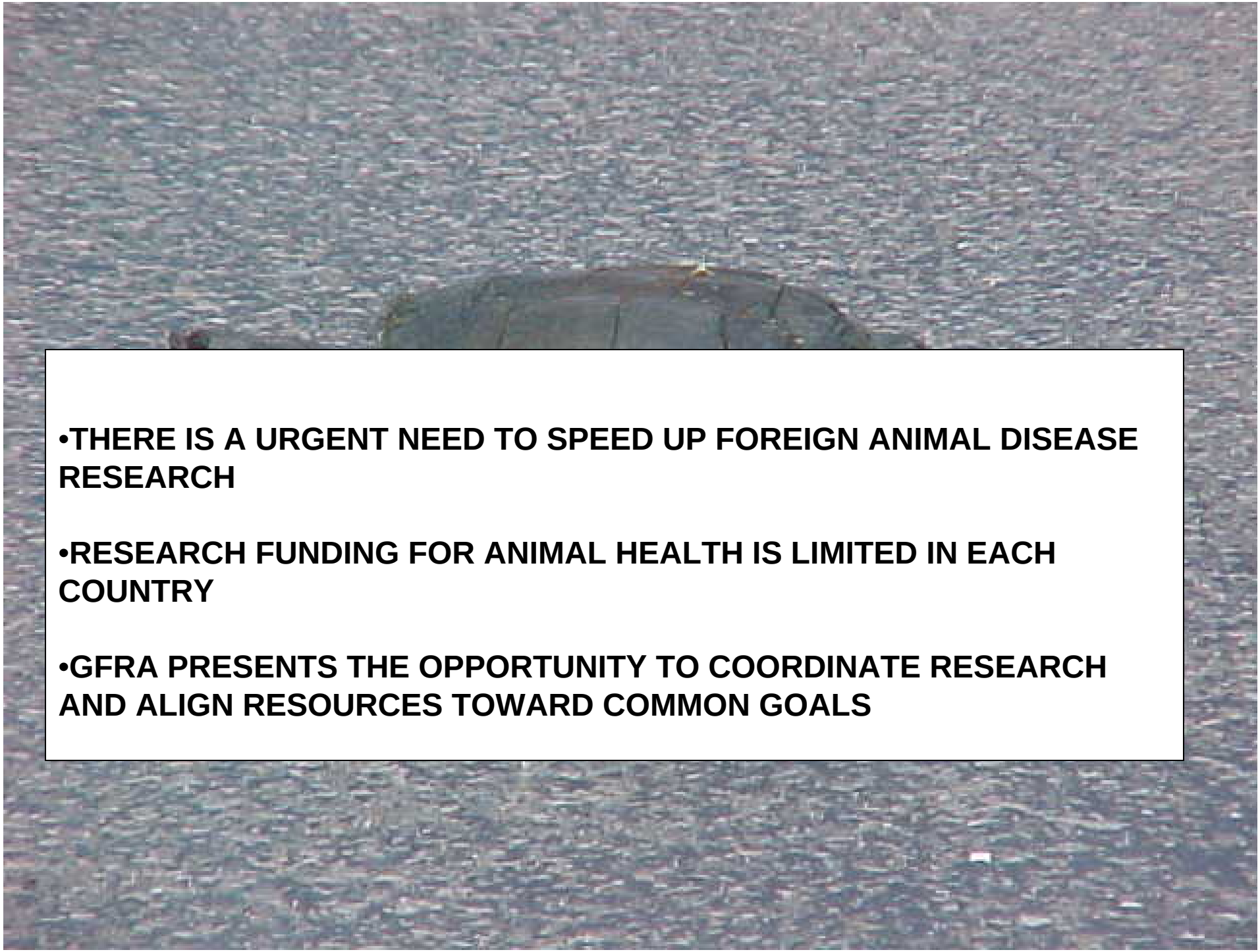
- Potency
- Onset and duration of immunity
- Prevention of carrier state
- Cross serotype protection

Plum Island GFRA-Related Collaborations

- **Institute of Animal Health Pirbright-UK**
  - Interaction between Ad5-FMD vector and bovine dendritic cells
  - Infectious copy FMD vaccines: marker and capsid stabilization
  - Virus host interactions – cattle and pigs
- **Canadian Food and Agriculture Institute, Winnipeg Canada**
  - Characterization of Monoclonal Antibodies to FMDV NSP
  - Improvement of Vesicular Disease Real Time RT-PCR
- **INTA-Argentina**
  - Developing predicting tools for prevention of FMD
  - Understanding Local and Systemic Protective Responses Against FMDV Infection in Cattle: A Genomics Approach
- **Department of Livestock Development – Thailand AND AAHL-CSIRO - Australia**
  - Molecular Epidemiology, Surveillance and Predictive Tools for FMD Control In Thailand

Other Collaborations –

- **ARRIAH (Russia)**. Investigation of emergent viruses and development of diagnostic tools for FMD
- **OVI – South Africa** – Improvement of FMDV SAT2 vaccines using recombinant FMDV
- **NARC- Pakistan –** Genomic Characterization of Local Viral Strains For Improving FMD Vaccines
- **CISA-INIA – Spain** – Innate Responses In FMDV-Infected Swine



- **THERE IS A URGENT NEED TO SPEED UP FOREIGN ANIMAL DISEASE RESEARCH**

- **RESEARCH FUNDING FOR ANIMAL HEALTH IS LIMITED IN EACH COUNTRY**

- **GFRA PRESENTS THE OPPORTUNITY TO COORDINATE RESEARCH AND ALIGN RESOURCES TOWARD COMMON GOALS**

Thank you!

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