The early pathogenesis of FMD and the implications for control measures

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Global Foot-and-Mouth Disease Research Alliance

USDA

OUTLINE

- Current FMD Vaccines – limitations – adequate for global eradication?
- FMD pathogenesis – recent lessons learned
- Approaches to use of pathogenesis data to rationally design the next generation of FMD vaccines.

Concerns with current FMD Vaccines

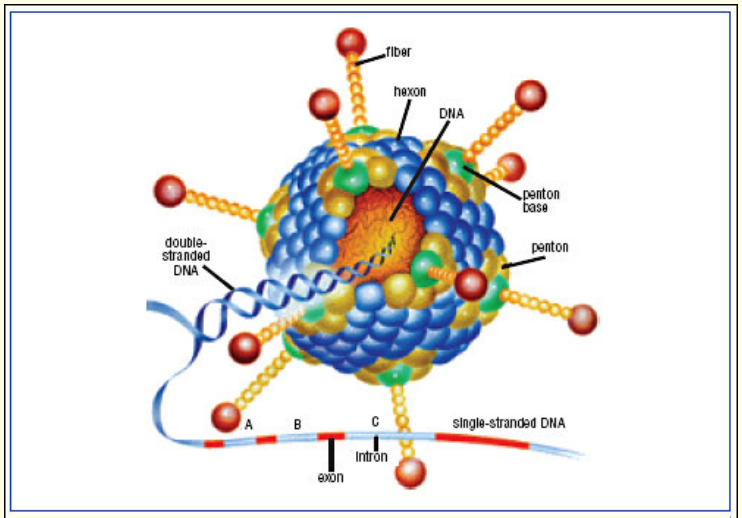
- Require adaptation and growth of large volumes of wild type virus in cells
- Escape of virus from manufacturing facilities
- Require banking of multiple antigen concentrates
- Some antigens lack stability (low potency/short shelf life)
- Short duration of immunity <6 months (?)
- Vaccinated and exposed animals become carriers
- Difficult to differentiate vaccinated from infected animals (DIVA) when NS proteins present

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 virulent FMDV
- Prevent development of carrier state
- Protection against multiple serotypes
- Stable antigen – long shelf life

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



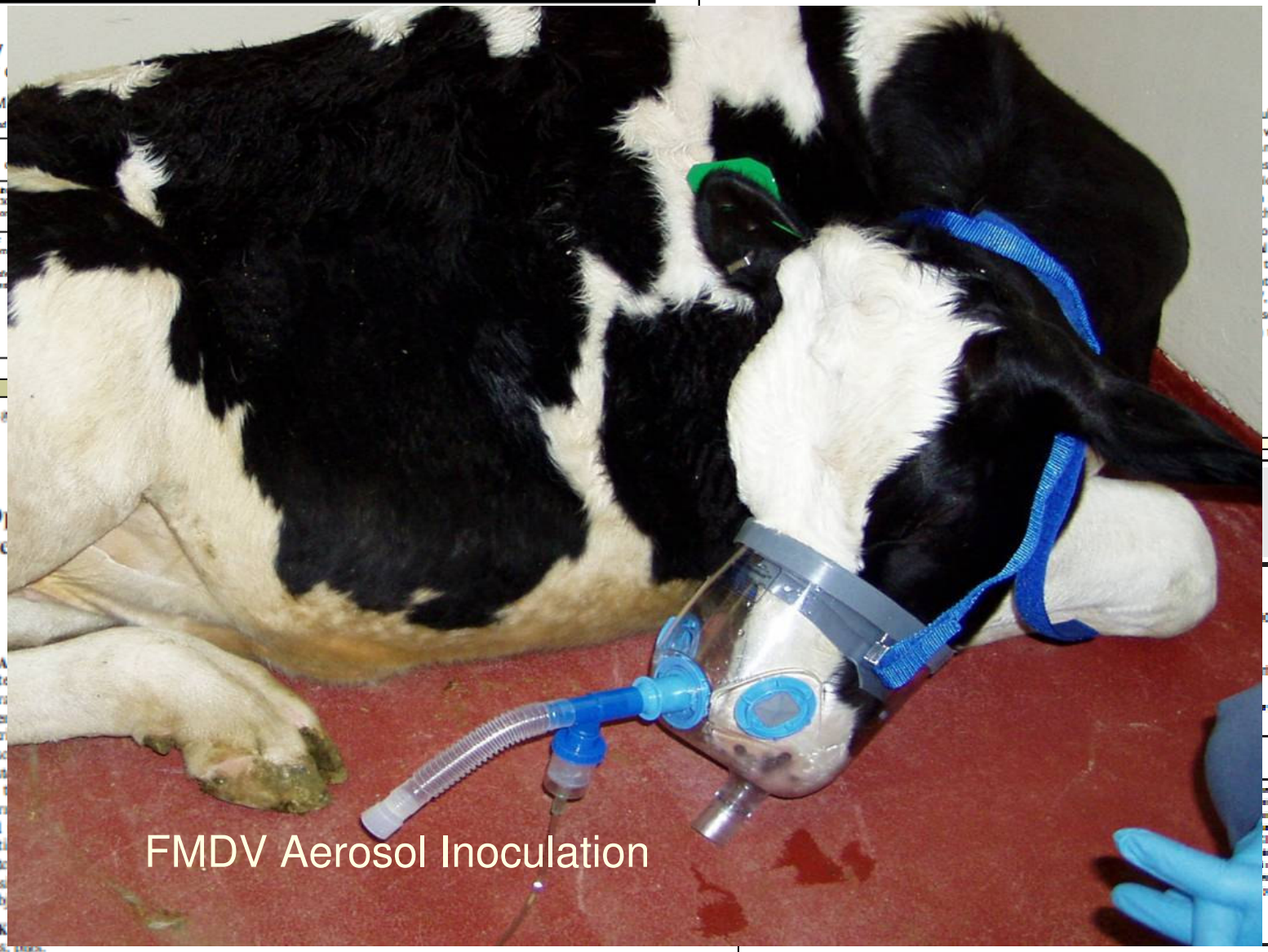
Human Defective Adenovirus 5 vector
- Lacks necessary proteins for growth
- Delivers and expresses transgenes in target cells

M. Grubman

FMD Vaccine Product Profiles: Current Inactivated vs. Ad5-FMD

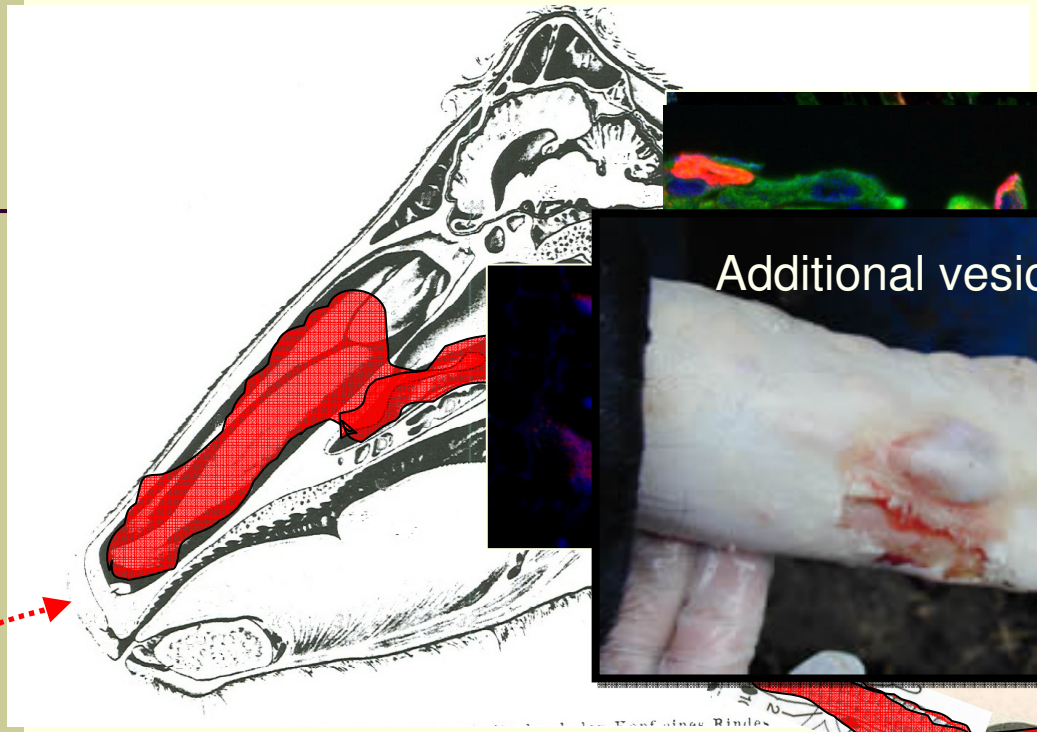
PRODUCT PROFILE	CURRENT INACTIVATED	Ad5-FMD
Prevents viral transmission	✓	✓
Early onset of immunity	✓	✓
Marked vaccine (DIVA capable)	+/-	✓
Domestic production (USA)	No	✓
Long-term stability formulated product	No	✓
Long term protection	No	No
Prevents primary infection (carrier state)	No	No
Provides cross-protection	No	No

FMD Pathogenesis 2010-2011

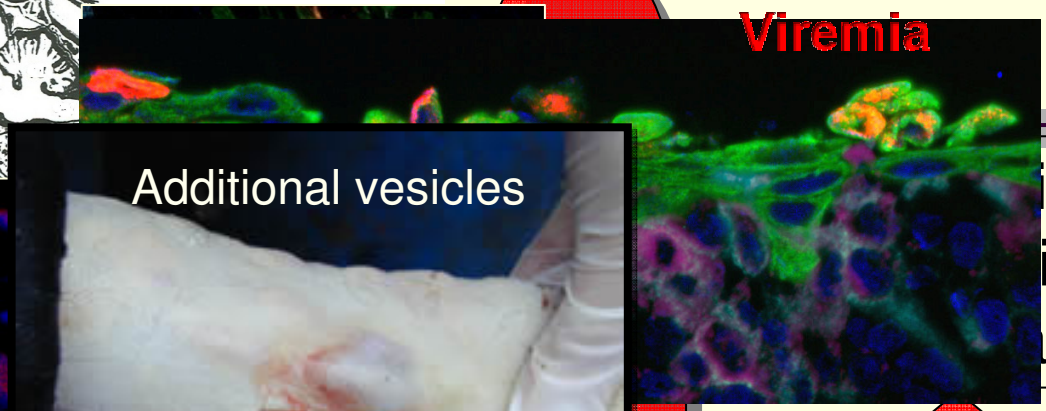


FMDV Aerosol Inoculation

Overview of FMD early pathogenesis in cattle



Peak Viremia



Additional vesicles

Aerosol Exposure

HPA

6 HPA

HPA

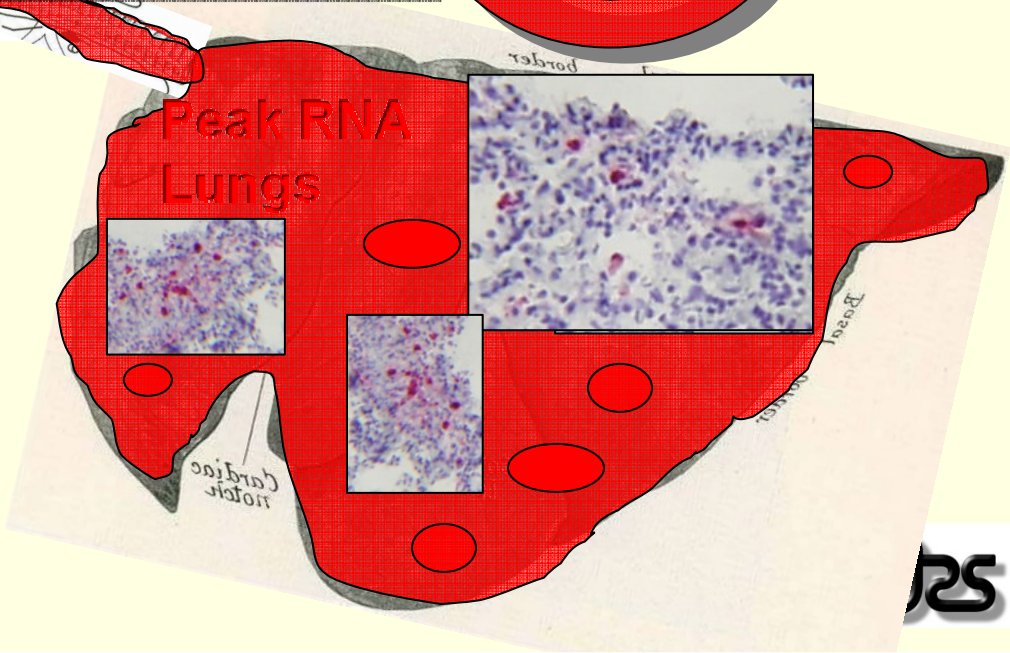
T = 48 HPA

HPA

T = 72 HPA

First vesicle

Peak RNA Lungs

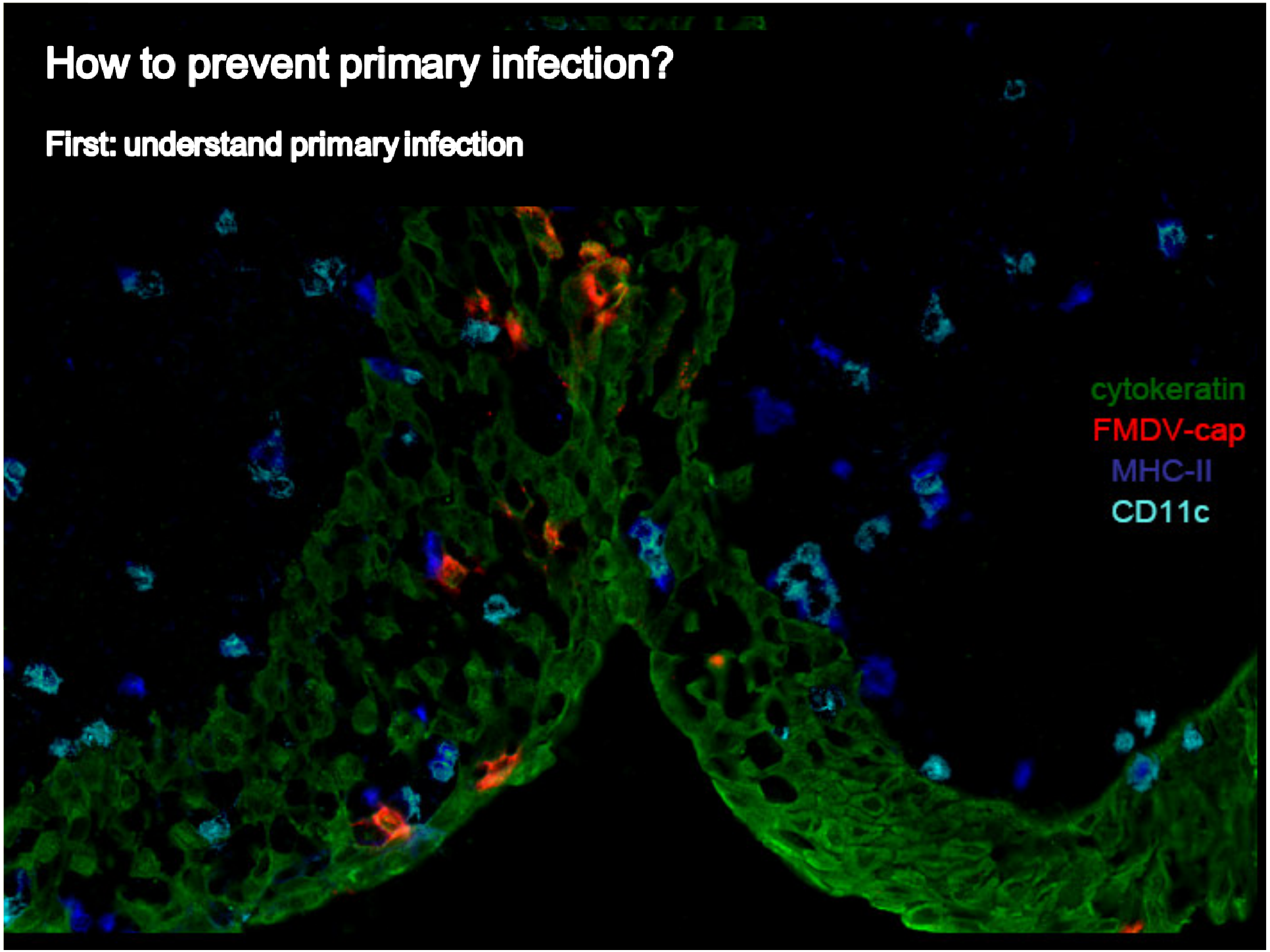


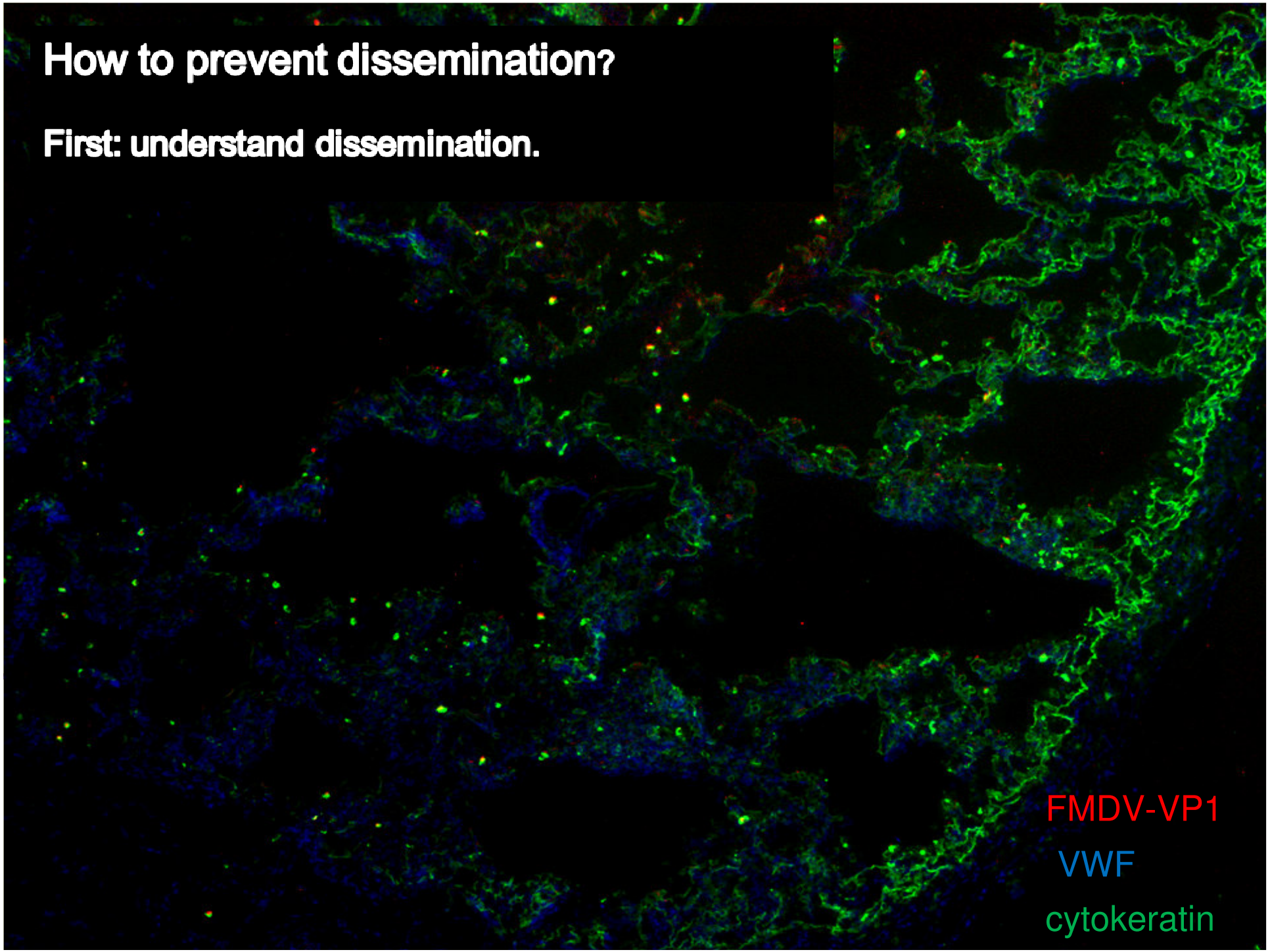
Rational Design: a new hope for better vaccines

- **Tissue-specific (process-specific) targeting of vaccines achieved through:**
  - **Identifying FMDV vulnerabilities through understanding novel, time-dependent virus-host interactions (*advanced progress*)**
  - **Designing products that target and exploit these critical vulnerabilities (*early progress*)**

How to prevent primary infection?

First: understand primary infection

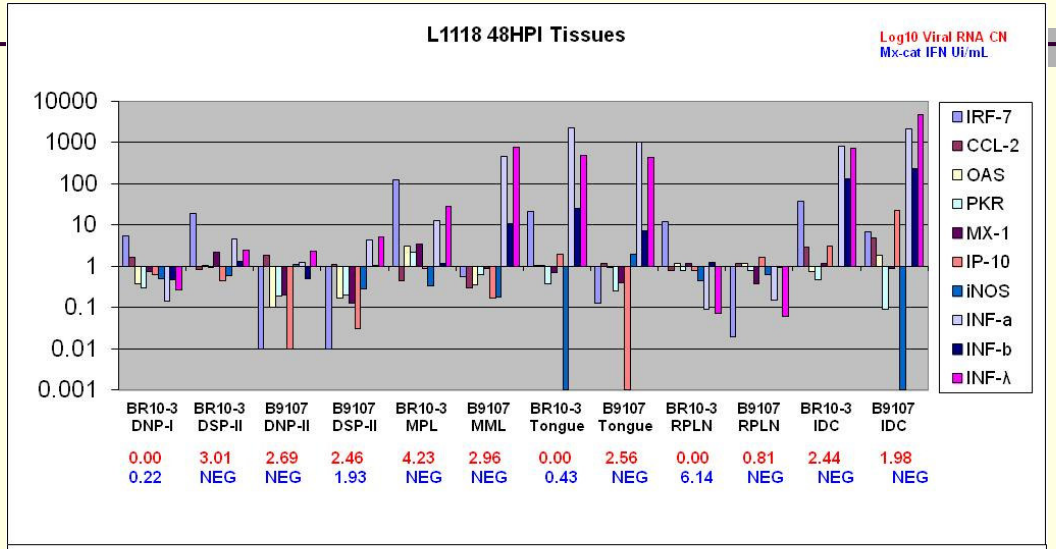


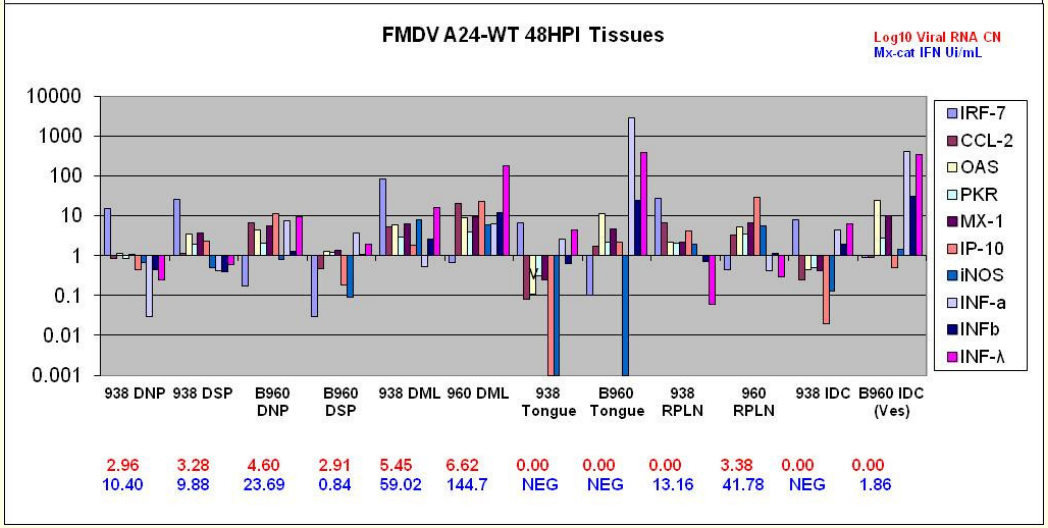

How to prevent dissemination?
First: understand dissemination.
FMDV-VP1
VWF
cytokeratin

The Hunt for Rational Design Targets (*molecular events*)

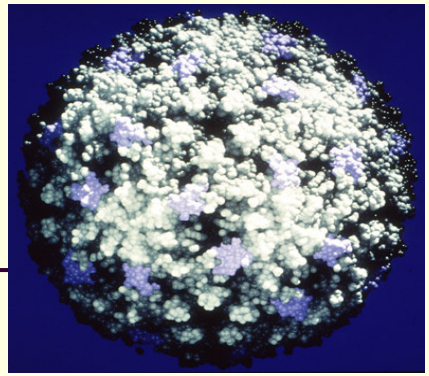
How to successfully modulate innate immune response?

First: understand innate immune response.

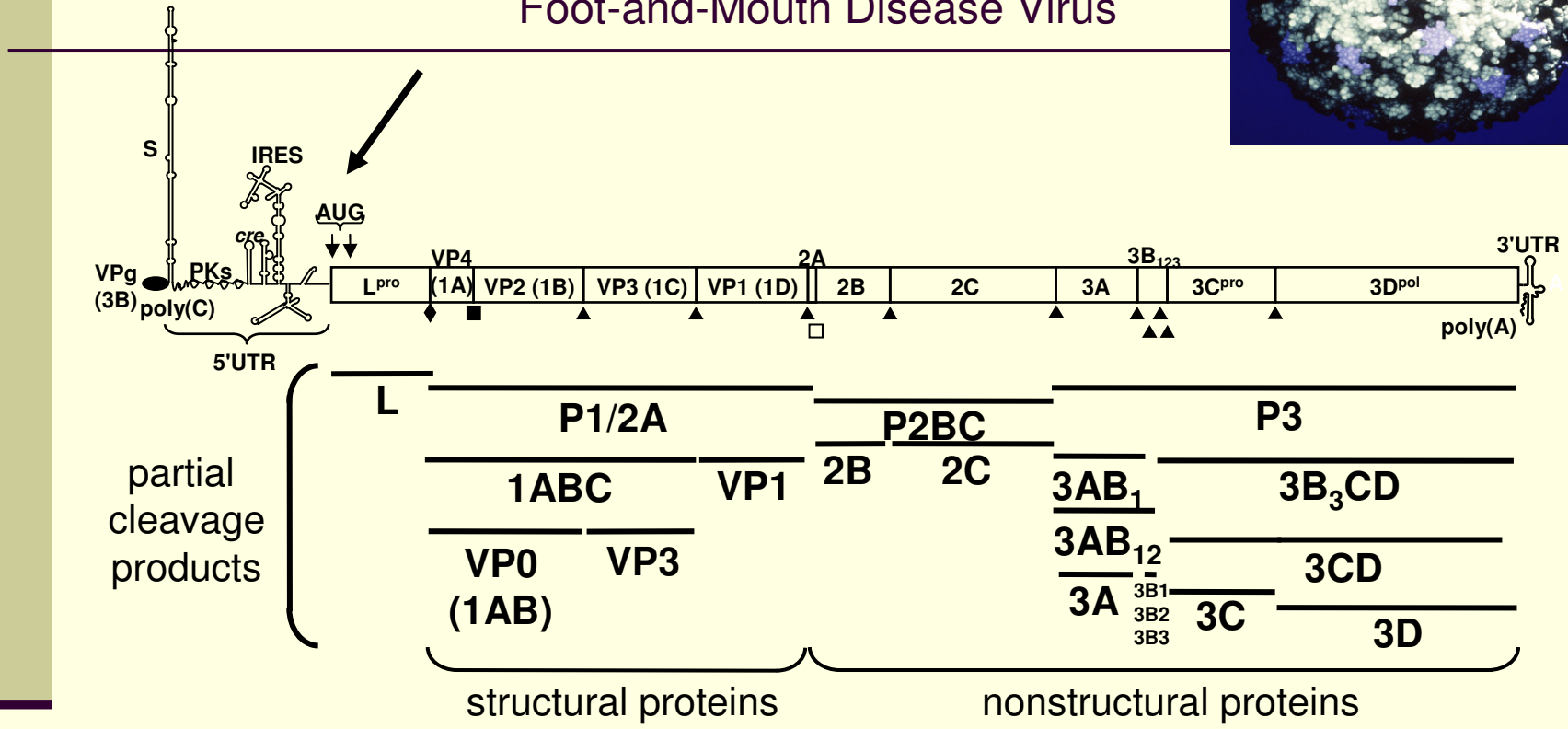




The Future of Rationally Designed FMD Vaccines



Foot-and-Mouth Disease Virus

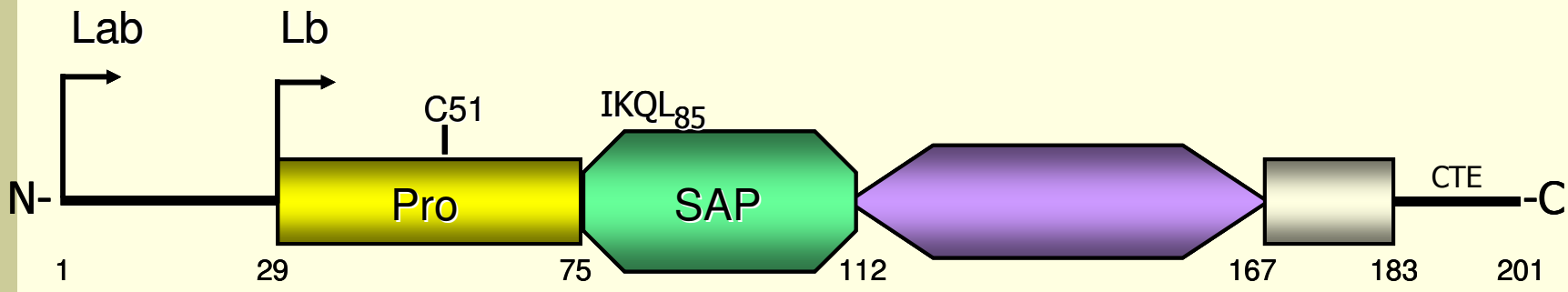


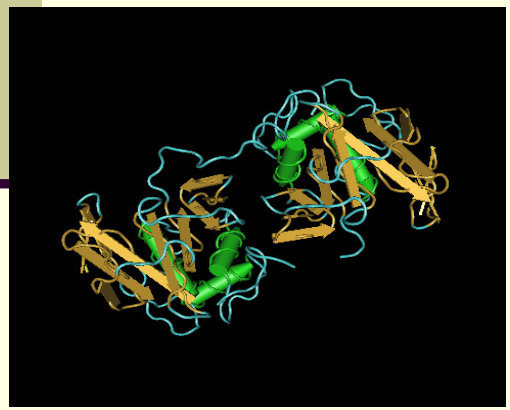
- Identification of genomic regions determining virulence
- Identification of antigenic epitopes associated to infection
- Engineering FMDV **to attenuate** and remove antigenic sites

Protease Cleavage Sites

L^{pro} ◆	unknown ■
2A □	$3C^{pro}$ ▲

L^{pro} structural domains



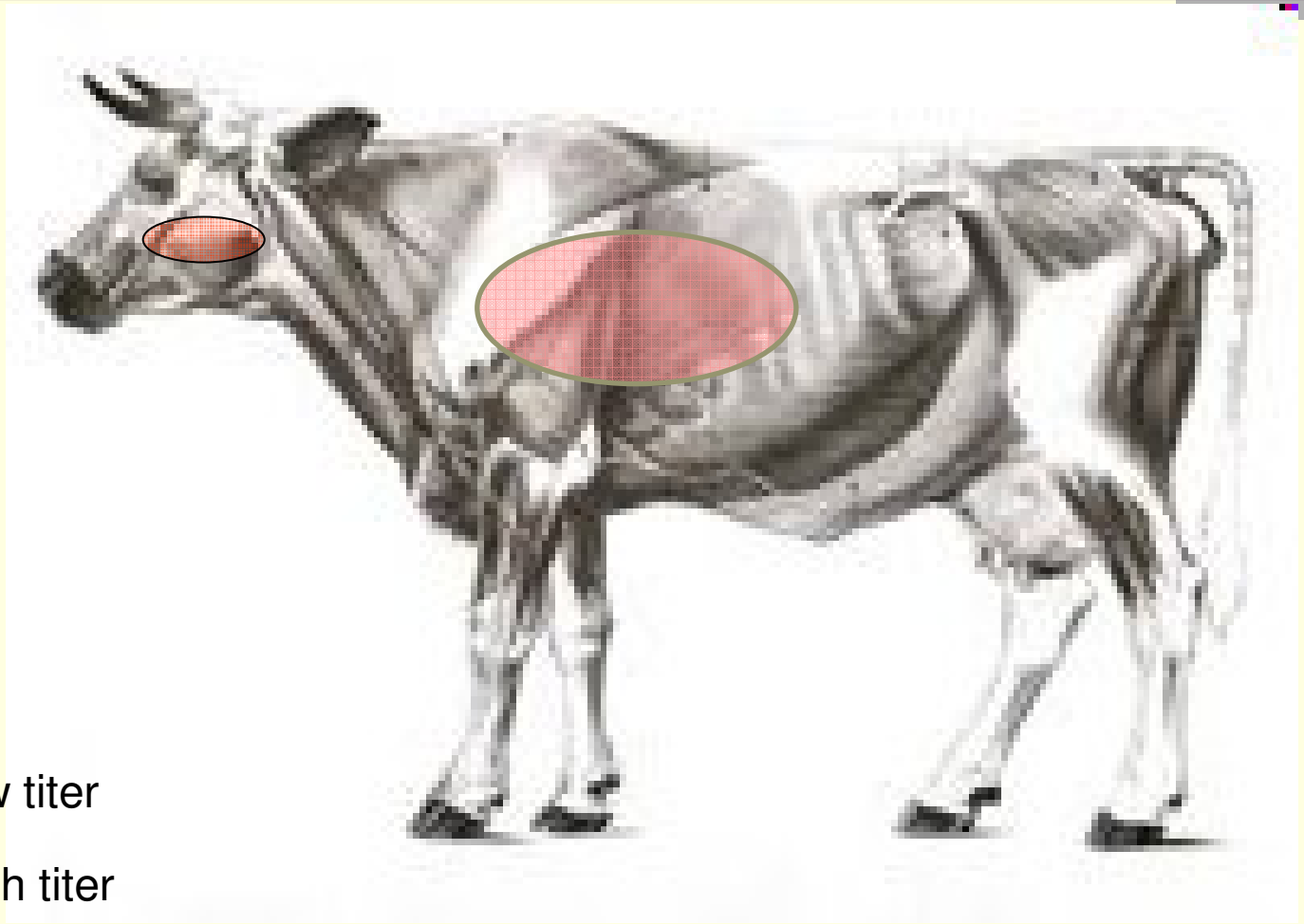


de Los Santos, et al, J. Virol 2009

- Protease domain previously identified – Cys 51 critical
- Lpro contains a putative SAP domain (SAF-A/B, Acinus, and PIAS)
  - *Nuclear retention and nuclear localization*
  - *DNA binding: present in nuclear proteins involved in chromosomal organization*
  - *Inhibit STATs (signal transducers and activators of transcription) signaling: PIAS (protein inhibitor of activated STAT) contain SAP domains*

FMDV Containing Mutations in Leader Become Attenuated In Cattle

6-24h 24-48h 72-96h 96-240h >28 days?



Low titer

High titer

Possible approach for LAV?

Safe Live Attenuated FMD Vaccines?

- Attenuated vaccines mimic viral life cycle in host
- Induce long lasting immunity (life long in some cases)
- Some success stories: Smallpox, Rinderpest, Polio.
- Concern: reversion to virulence

Challenges For FMD Vaccines

- Understand the barrier of serotype- and subtype-specific vaccine protection (achieving cross-protection and/or increasing the breadth of antigenic coverage)
- Improve the onset and duration of immunity of current and next generation FMD vaccines
- Target FMD vaccines to induce protection at relevant tissues to prevent infection (hence also prevent persistence)

There is a need for vaccines that are inexpensive to produce, easy to deliver and induce long-term immunity. Also there is need for better integrated strategies that fit the specific needs of endemic regions. Only when these critical components are available will the global eradication of FMDV be possible

Collaborative research can improve the lives of millions of people around the globe!


U.S. Department of Homeland Security
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Thank you !!!

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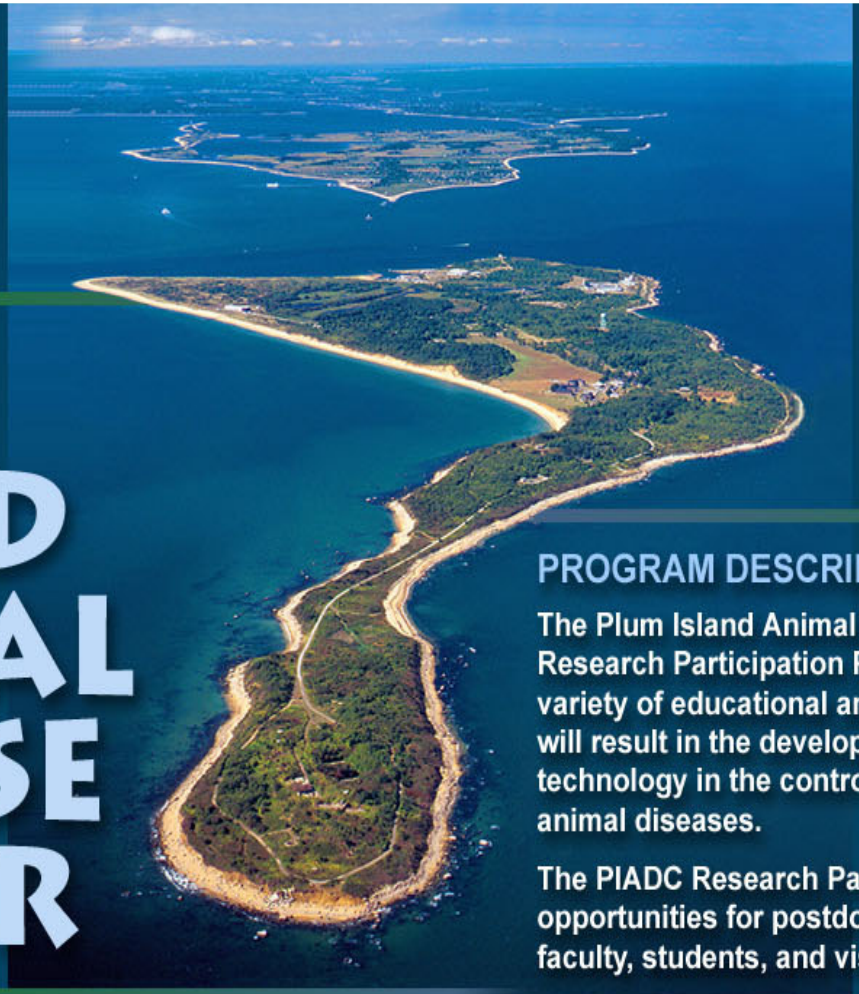

Research Participation Program

Administered by Oak Ridge Institute for Science and Education.

PROGRAM DESCRIPTION:

The Plum Island Animal Disease Center (PIADC) Research Participation Program aims to provide a variety of educational and research opportunities that will result in the development of new knowledge and technology in the control and eradication of foreign animal diseases.

The PIADC Research Participation Program will provide opportunities for postdoctoral fellows, postgraduates, faculty, students, and visiting scientists.

AREAS OF STUDY:

Veterinary medicine, pathology, immunology, molecular biology, virology, epidemiology, or other disciplines related to foreign animal diseases.

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