FMD: Current Situation of Research and Research Needs

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OIE/FAO Global Conference on FMD, 24-26 June 2009, Paraguay

BBSRC bioscience for the future

Institute for Animal Health

Talk overview

- FMD research past and present
- Options, priorities and gaps
- Importance of novel vaccine development and underpinning immunological research
- How to deliver what is needed

What do we mean by “Research”

- Systematic investigation
  - to discover better tools and options for FMD control

- Surveillance
- Applied research – utilising knowledge to achieve goals
- Basic research – developing new knowledge

Context and opportunities arising from wider research and development

- Technological developments
  - miniaturisation
  - chemistry
  - computing
- Advances in biological sciences
  - viral and host mechanisms
  - reverse genetics
  - expression systems
- Advances in mathematical biology
  - systems biology

FMD Research Highlights

Friedrich Loeffler
(1852 – 1915)

1898 – Filterable agent - Loeffler & Frosch*

1920 – Guinea pig model – Waldman & Pape*

1920's – Transfer of protection through serum

1940's – O, A, C serotypes – Vallee & Care / Waldman*

1947 – Virus growth in tongue epithelium – Frenkel*

1965 – BHK suspension cell culture growth - Capstick

1974 – BEI inactivated vaccine – Bahnemann

1980's – ELISA for virus and antibody detection

1987 – Sequence based subtyping – Beck & Strohmeier

1990's – RT-PCR diagnosis

*Cited by Brown F (2003) Virus Research

Recent successes

- High throughput lab diagnostic capability in labs
- DIVA diagnostics in place and capability understood
- Pen-side tests becoming a reality

- Fine-scale tracing by whole genome sequencing
- Epidemic modelling as a decision support tool

- Viral receptors in vivo and in vitro defined
- Viral persistence in lymph nodes mapped to follicular dendritic cells

- Adenovirus vectors delivering interferons and FMDV proteins
- Stabilised virus-like particles (VLPs) and large-scale production of VLPs
- Orally effective anti-viral demonstrated in pigs

What are the priorities and gaps?

- Shared and disparate priorities for countries free and infected with FMDV

- Royal Society Report (UK, 2002)
- EUFMD Research Group Open Meeting Recommendations (latest - Erice, 2008)

- DISCONTOOLS (2008-2011, continuing ETPGAH)
  - **Disease Prioritisation**, **Gap Analysis** and the use of **New Technologies** in the field of animal health research

Funders also invest in FMD Research to maintain expertise and capability

Global roadmap for improving the tools for FMD control in endemic settings (GFRA 2006)

- Two principal priorities both requiring a combination of basic and applied research
- Better vaccines
  - the ideal and what would be enough to make a difference
  - likely success, timescale and expense
- Better understanding of animal production systems and FMD dynamics within them
  - epidemiological studies to identify critical control points and alternatives to mass vaccination
  - cost-benefit of disease control

Research needs - Diagnosis

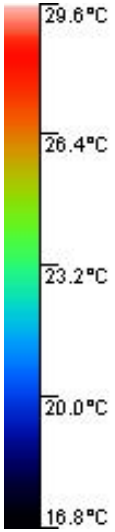
- Good lab tests available
- Increasing reliance on recombinant antigens, monoclonal antibodies and nucleic acid-based approaches
- Faster, simpler, safer, more reliable, better validated
- New platform technologies
- Further developments in field detection

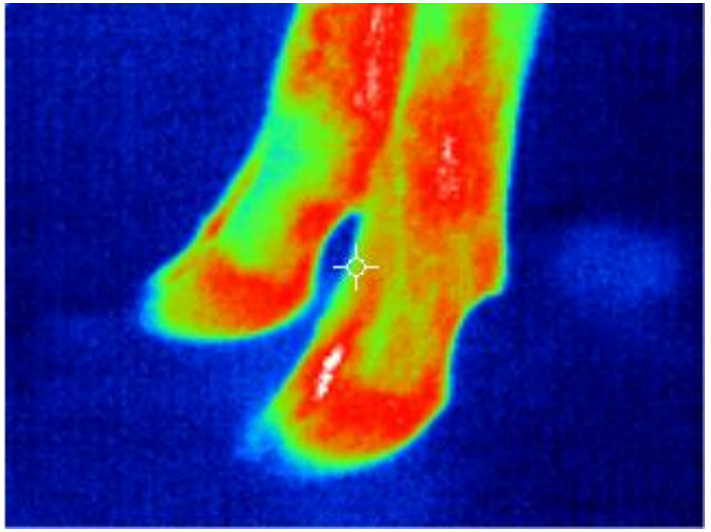
Rapid detection of FMDV in the field

SVANODIP® FMDV-Ag

Mesosystems: non-invasive air samplers

Smiths Bio-Seeq™





Infra-red thermography

Research needs - Epidemiology

- Tracing and predicting – determinants of virus spread and persistence
- Field, molecular and experimental epidemiology
- Development of models - biology with mathematics

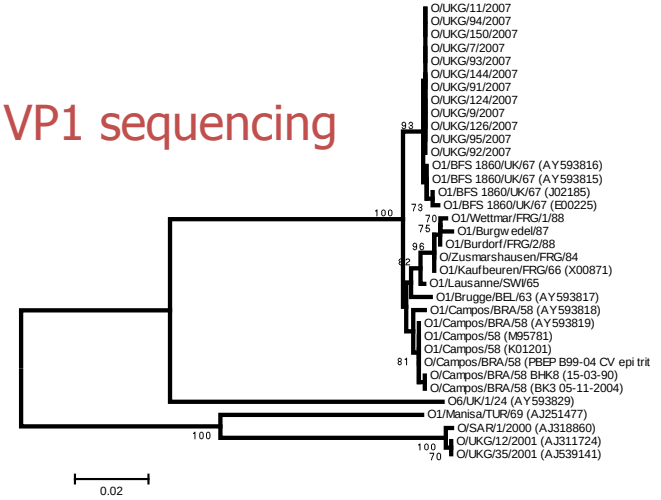
- Some questions
  - Minimum doses by different routes?
  - Role of different host species?
  - Determinants of viral evolution?
  - Differences in the epidemiology of different FMDVs?
  - Networks of contacts and definitions of epidemiological units?
  - Key parameters and their values for models?

- A significant funding gap identified by GFRA

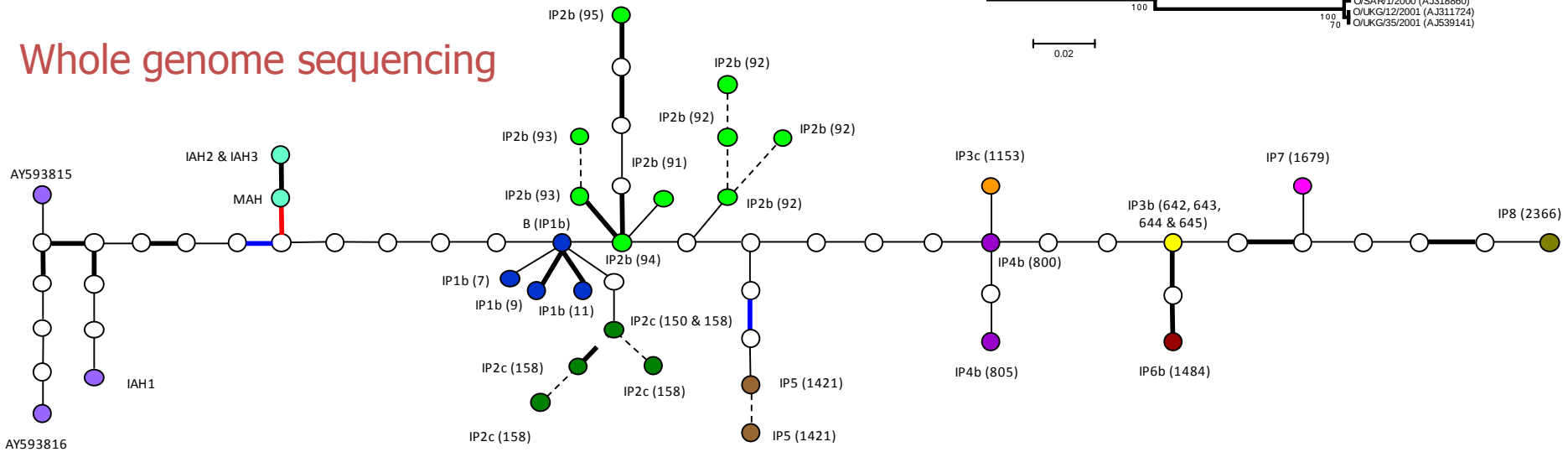
Potential for fine tracing and identifying missing links

UK 2007 outbreak phylogeny

VP1 sequencing



Whole genome sequencing



No. of genomes = 26

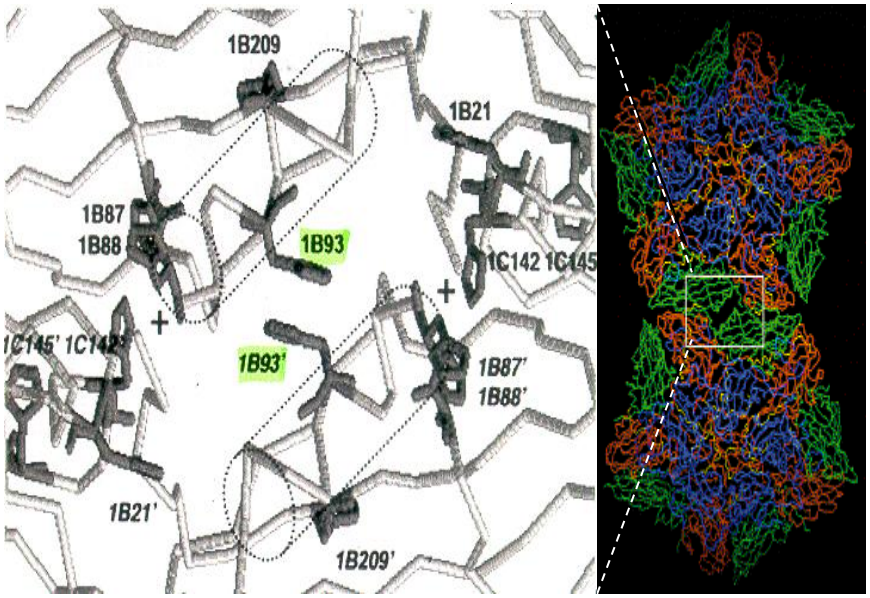
Cottam *et al* 2008 PLoS Pathogens 4, 1-8

Research needs – Host/Pathogen Interactions

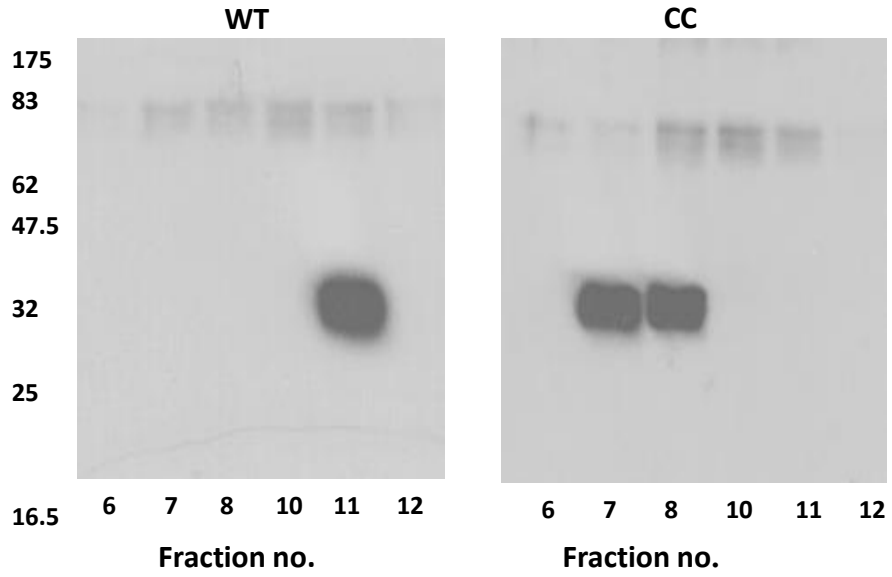
- Viral structure and mechanisms
- Viral and host determinants of virus replication, pathology and protection
  - Which proteins and signals can elicit protection ?
  - Need for / ways to stimulate mucosal and T cell immunity
  - How to elicit immune memory to FMDV
  - Correlates of protection
- A major funding gap identified by GFRA

Covalent cage mutation to stabilise capsid

Substituting His 93 of 1B(VP2) for Cys allows disulphide bridge formation, cross-linking adjacent VP2 units



Survival of covalent cage (cc) but not wild type (wt) capsids treated for 2h at 56ºC (or for 30min at pH5), then subjected to sucrose density gradients.



Persistence of non-replicating FMDV associated with follicular dendritic cells in lymph node germinal centres – a probable basis for sustained immunity following infection

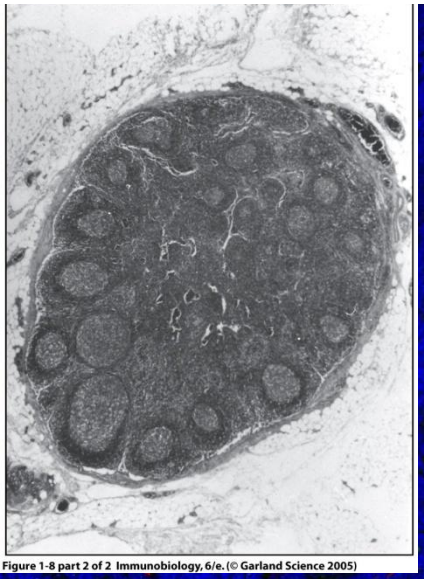
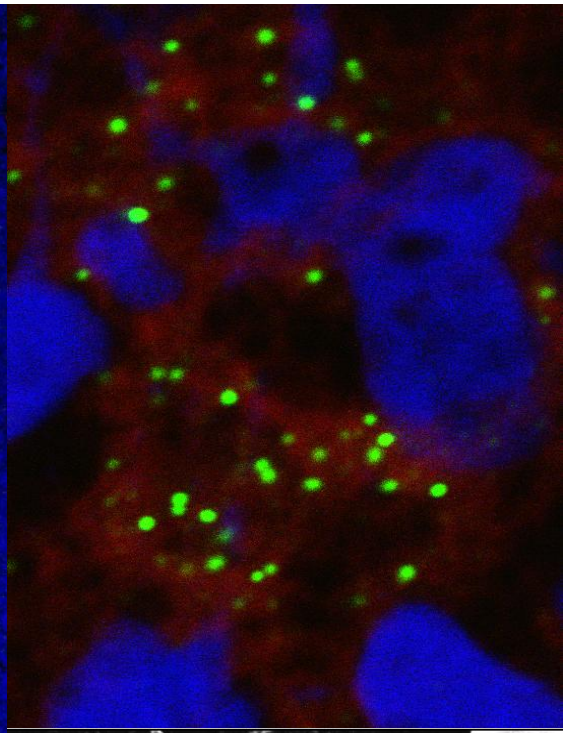
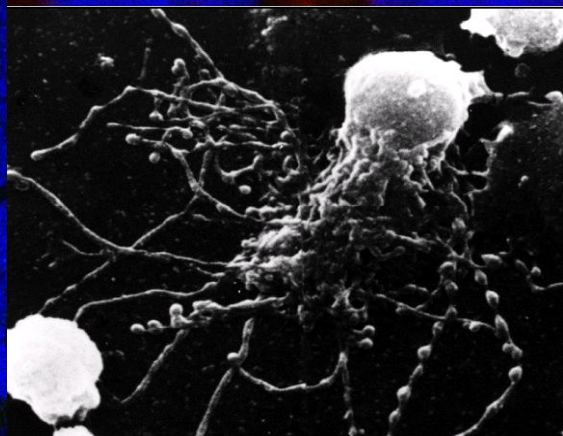


Figure 1-8 part 2 of 2 Immunobiology, 6/e. (© Garland Science 2005)





Juleff *et al* 2008 PLoS One

Research needs – Interventions

- Vaccine selection and cross-protection
- Vaccine development and evaluation

- Anti-virals based on innate immune mimetics and other mechanisms

- Decision support tools - where, when, what to test, vaccinate, cull, etc

KBBE-2008-1-3-02: FMD: improve and/or develop vaccines, vaccination strategies and diagnostics assays for free and endemic settings

EU FP7 DISCONVAC

1) Substitution of vaccine potency tests
2) Assessment / improvement of heterologous vaccinal protection
3) Development of vaccines / anti-virals with rapid onset / long duration
4) Improvement in 'DIVA' tests
5) Improving knowledge on FMDV transmission in recently vaccinated animals
6) Development or adaptation of computerised FMD-spread models to optimise vaccination schemes.

An explicitly expected impact to: Contribute to the Global FMD Research Alliance and to the Global Roadmap for Improving the Tools to Control FMD in Endemic Settings.

- http://www.endemicfmdroadmap.net/

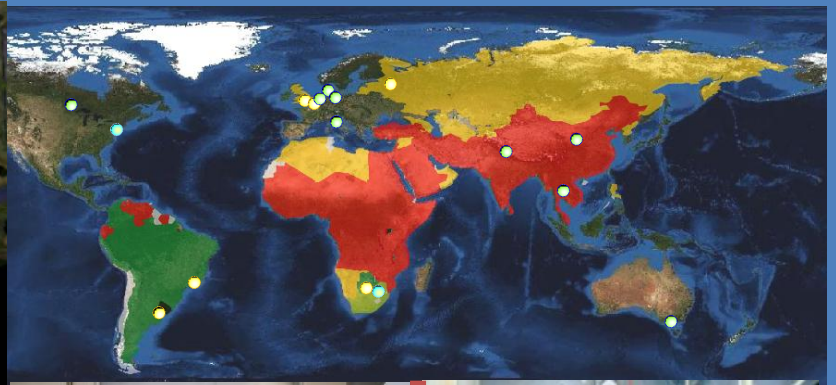
Better vaccines are a top priority

- Safer production
- Thermostable
- Longer duration of protection
- Rapid onset of protection
- Better markers

A thermostable vaccine producing long-lasting protection would reduce dependence on veterinary services for global disease control

Development of broad-spectrum FMD vaccines is a more distant prospect requiring elucidation of the viral determinants of B and T cell induced protection

Working with FMD requires costly facilities



- But facilities not enough
  - need money left over for projects and expertise
  - and danger of scientists themselves becoming isolated

How to deliver?

- Long term nature of threat means
  - worth investing for the future by developing new tools
- Maintain momentum built up since 2001
- Embrace reinforcement of effort from Asia
- Ambitious multidisciplinary approaches required
  - avoid isolation and tinkering
  - need FMD scientists linked to cutting edge science elsewhere
  - importance of wet and dry science - mathematical biology and epidemiology
- Facilities and research are expensive
  - focus effort, avoid duplication and maximise utilisation
  - should be multi-national centres and programmes
  - need for cost-benefit analyses to persuade funders
- Strengthen collaboration at all levels between funders, industry, researchers

Global Foot-and-Mouth Disease Research Alliance

Vision of GFRA

A coordinated global alliance of scientists producing information and innovation to enable the progressive control and eradication of foot-and-mouth disease

Mission of GFRA

To establish and sustain global research partnerships to generate scientific knowledge and discover the tools to successfully prevent, control and eventually eradicate foot-and-mouth disease

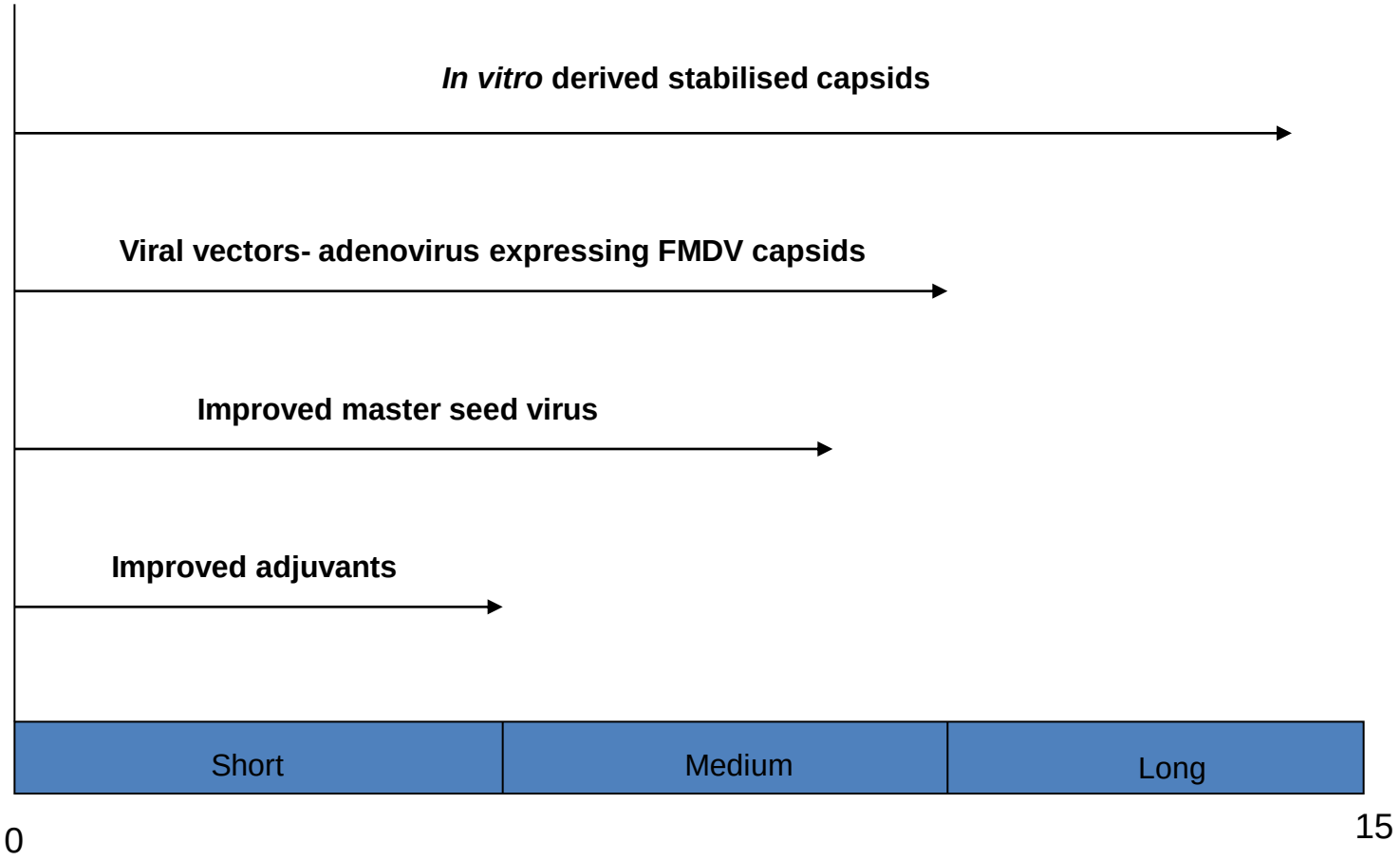
The problems are too great to tackle alone.

GFRA, therefore, aims to build a consortium of institutions conducting research into FMD to provide the scientific evidence and tools needed to control FMD in both FMD-free and FMD-endemic countries.

Only by maximizing the available resources and expertise, through international collaboration, can FMD be tackled effectively in the future.

Global FMDV research alliance

Co-ordinated effort to develop novel FMDV vaccines



Acknowledgements

- Colleagues and supporters of IAH FMD Programme
  - BBSRC, Defra, EC
- EC DG Research
  - FP6 Coordinated action for FMD & CSF (WP1 Research)
  - FP7 Disconvac
- The Global FMD Research Alliance
- The EUFMD Research Group

Apologies to those whose favourite research has been ignored - I only had 20 minutes!