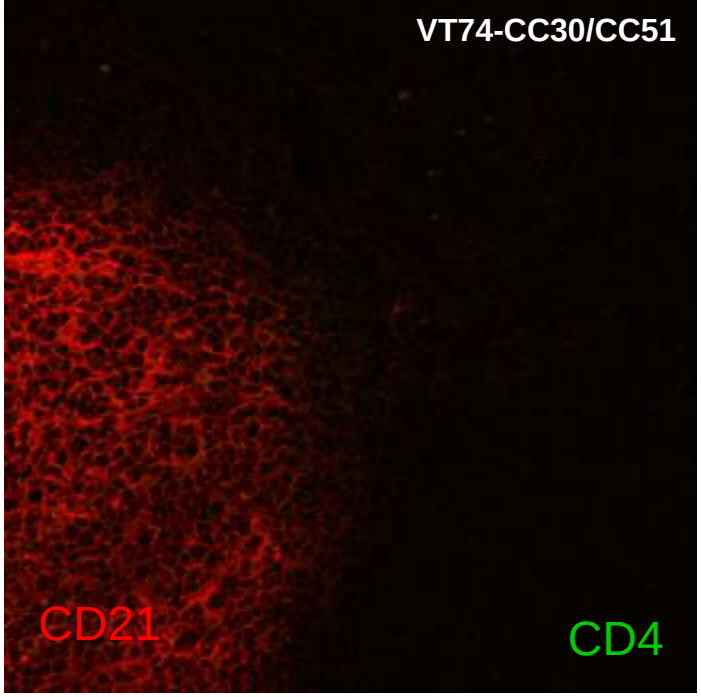
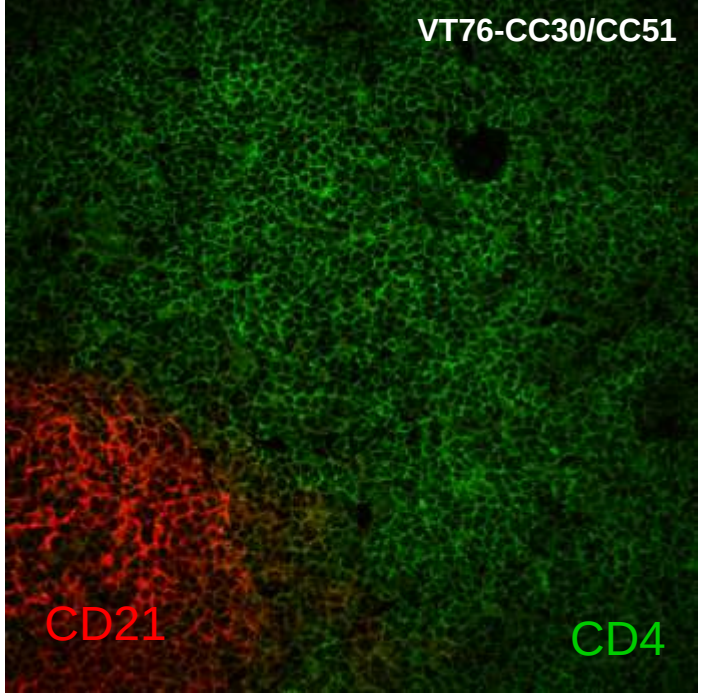
FMDV immunology to improve vaccines and vaccination

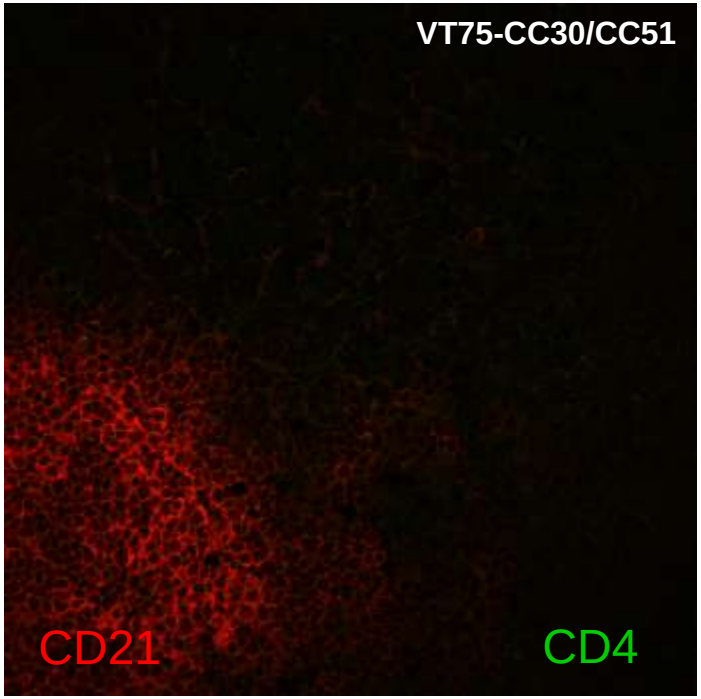
Early induction of neutralising antibodies

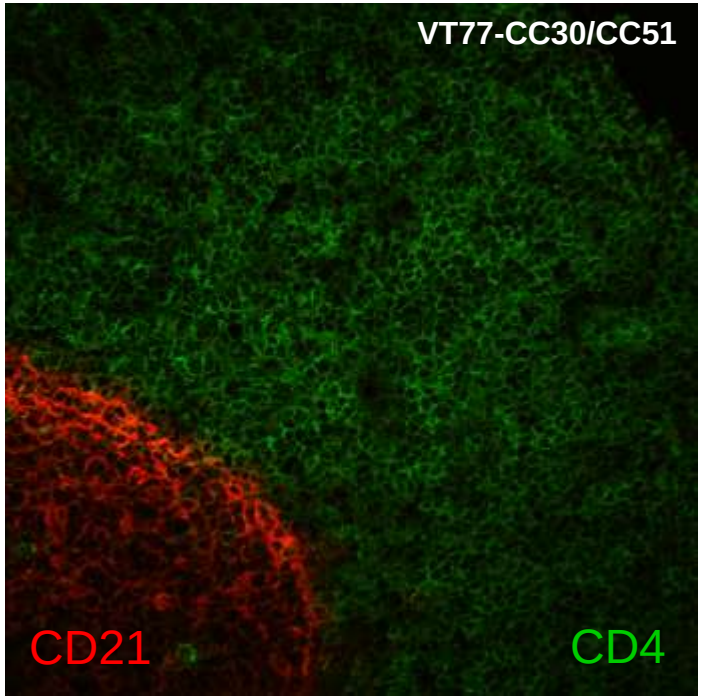
- suggesting a T-cell independent antibody response

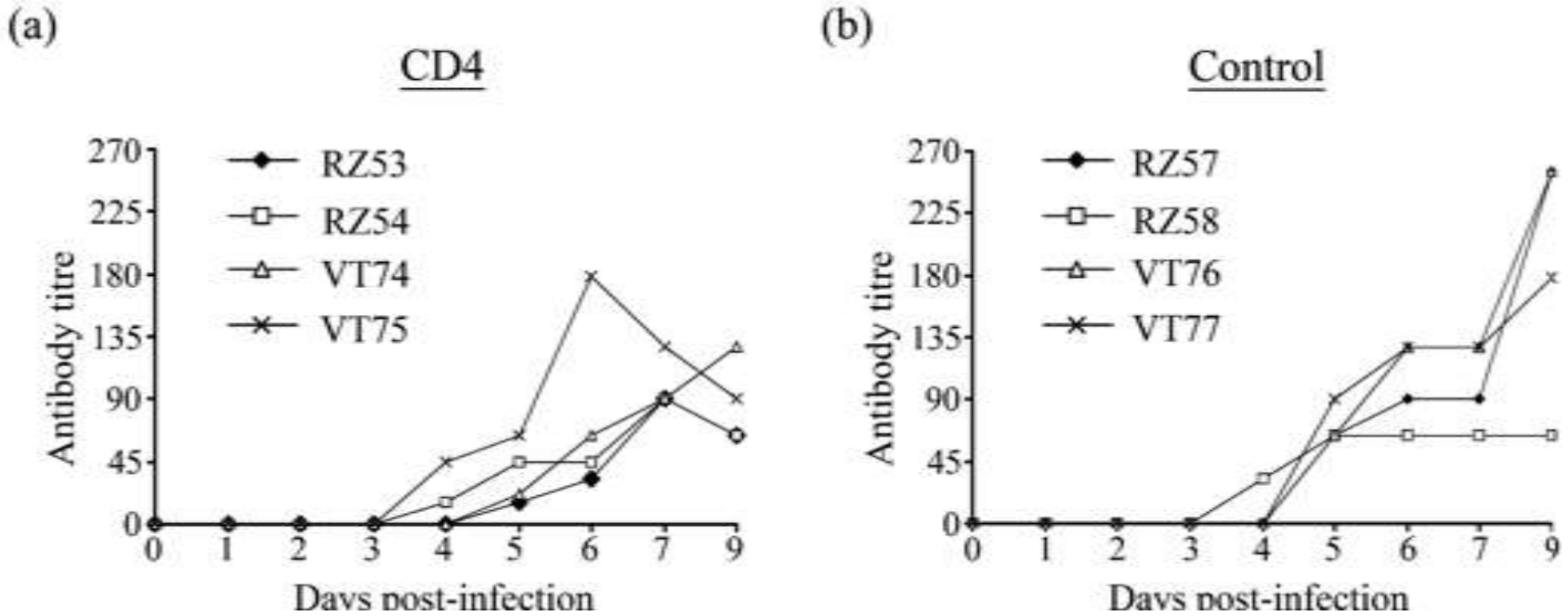
Depletion of $CD4^+$ T cells during acute infection with FMDV


VT74-CC30/CC51
CD21
CD4

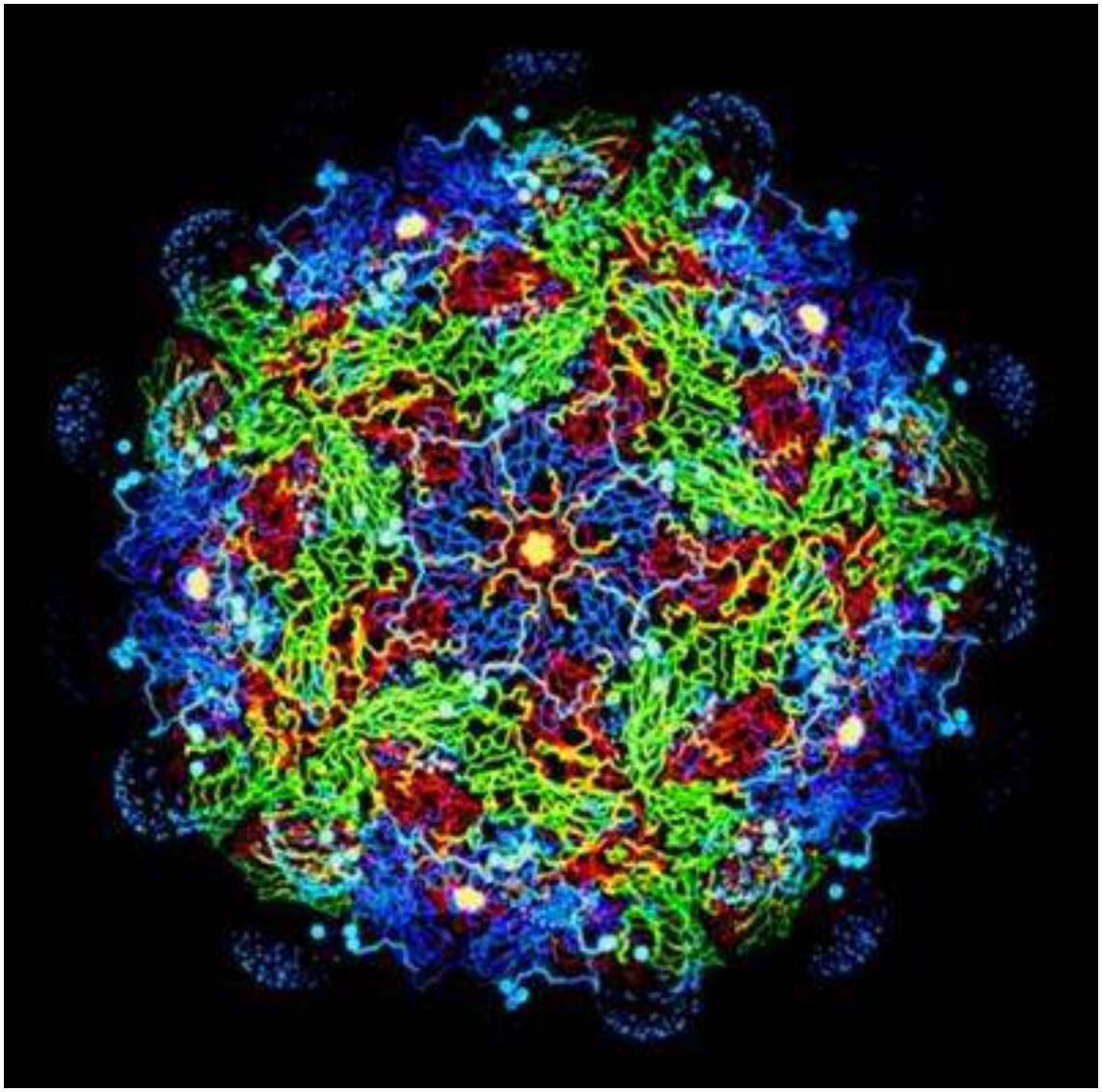

VT76-CC30/CC51
CD21
CD4


VT75-CC30/CC51
CD21
CD4


VT77-CC30/CC51
CD21
CD4

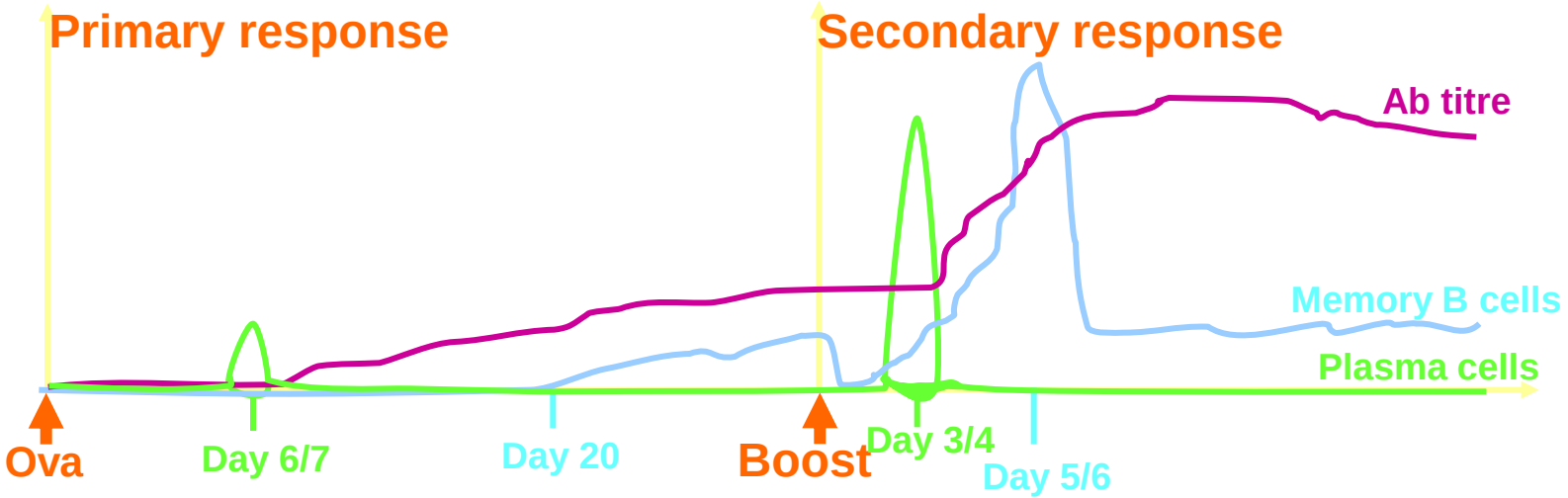

(a)
CD4
RZ53
RZ54
VT74
VT75
Antibody titre
270
225
180
135
90
45
0
0 1 2 3 4 5 6 7 9
Days post-infection
(b)
Control
RZ57
RZ58
VT76
VT77
Antibody titre
270
225
180
135
90
45
0
0 1 2 3 4 5 6 7 9
Days post-infection

FMDV capsid: T independent and T dependent epitopes

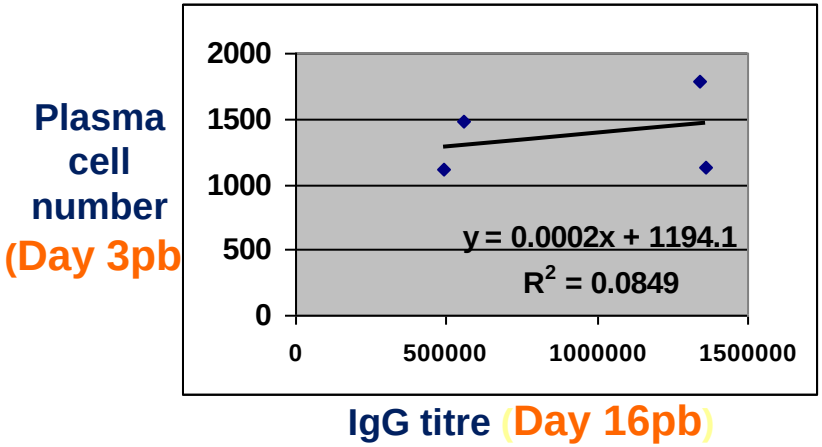


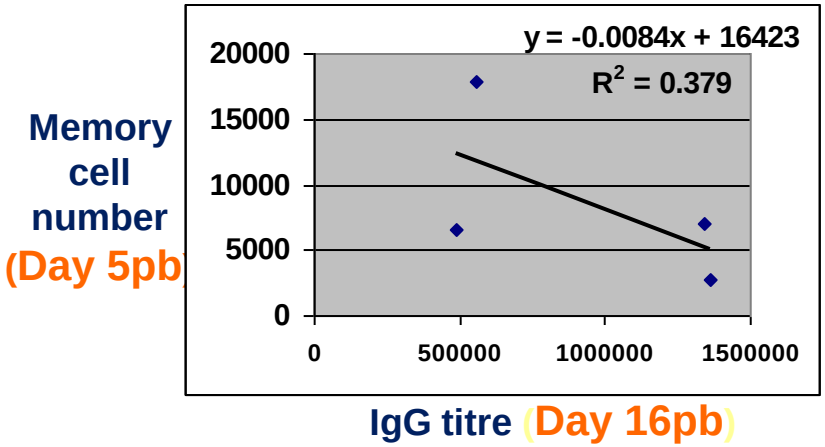
Outcome of this experiment

❖ Determination of the kinetics of plasma cells, memory B cells and Ab titre in the blood following immunisation (and boost immunisation) with ovalbumin:



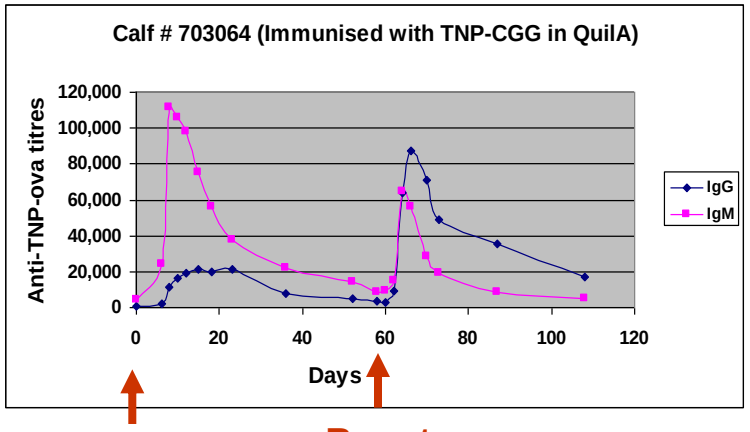
❖ No correlation between the Ab titres and the peak number of plasma cells or memory B cells generated.

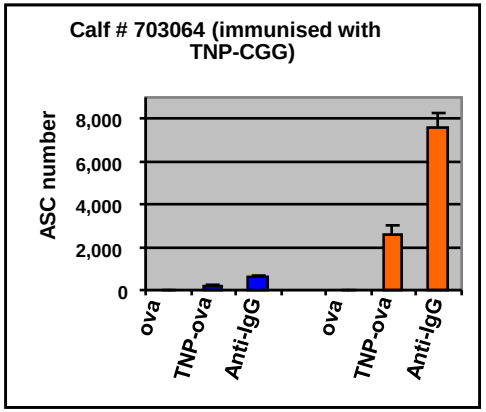




T-dependent vs T-independent responses

TD Response

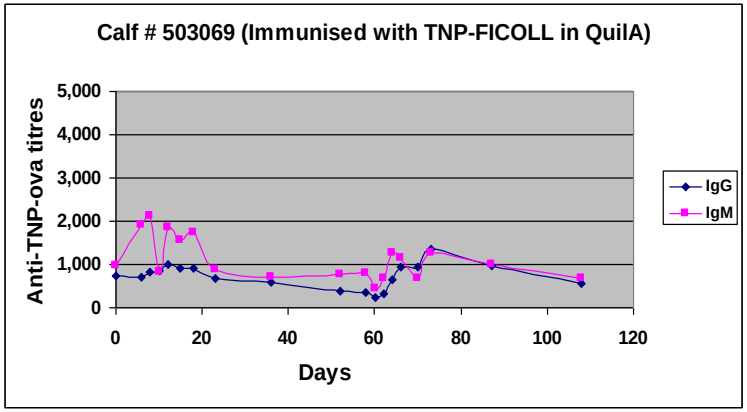


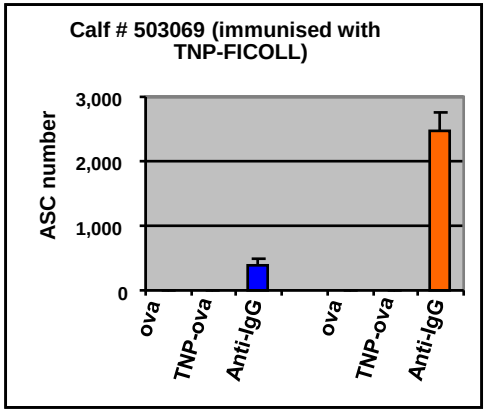


Immunisation

Boost (day 58)

TI Response





Immunisation

Boost (day 58)

Plasma cells (day 4pb)

Memory B cells (day 6pb)

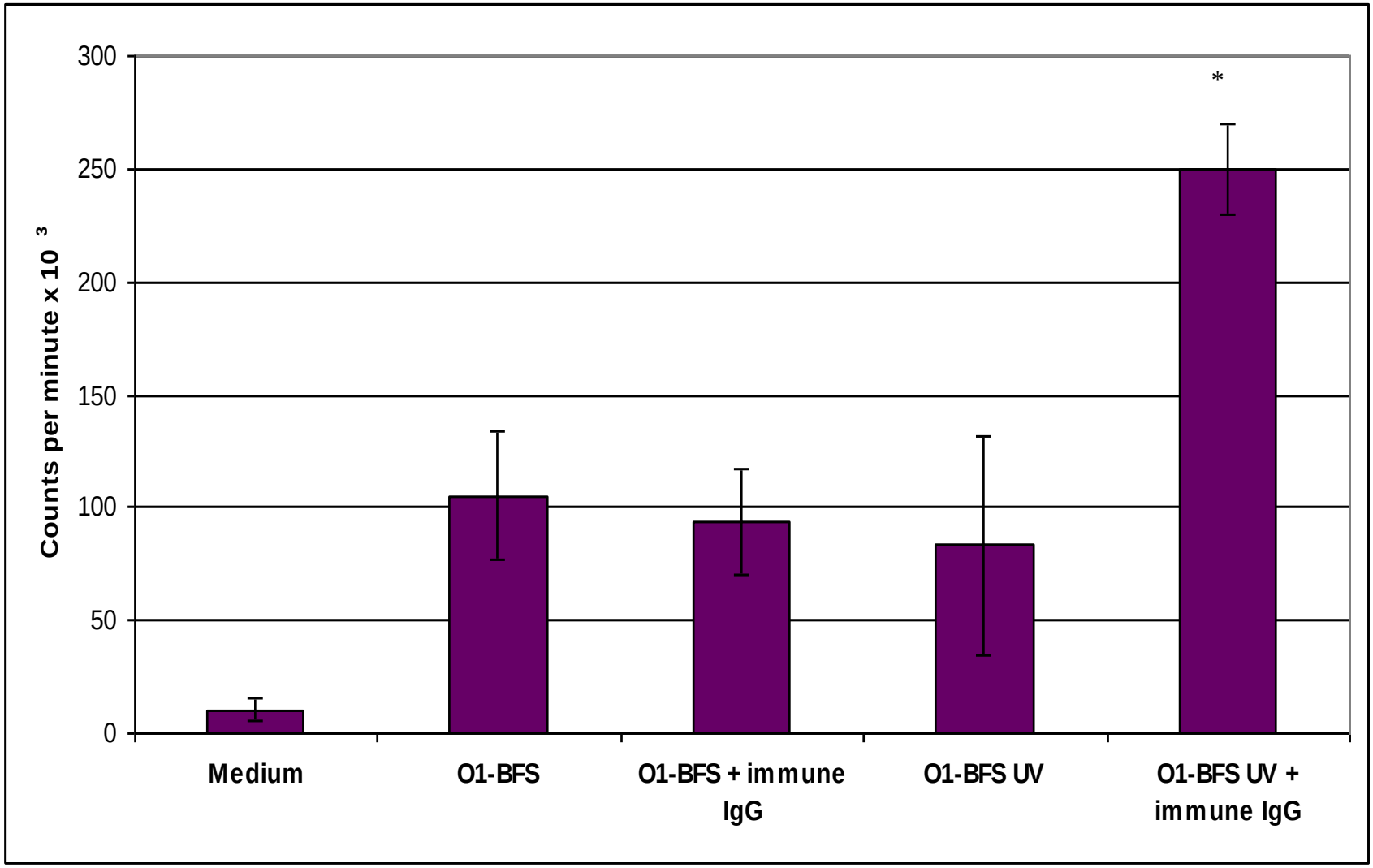
Immune response to vaccination

- rapid induction of antibody
- variable/ short duration of immunity
- variable CD4 T cell response

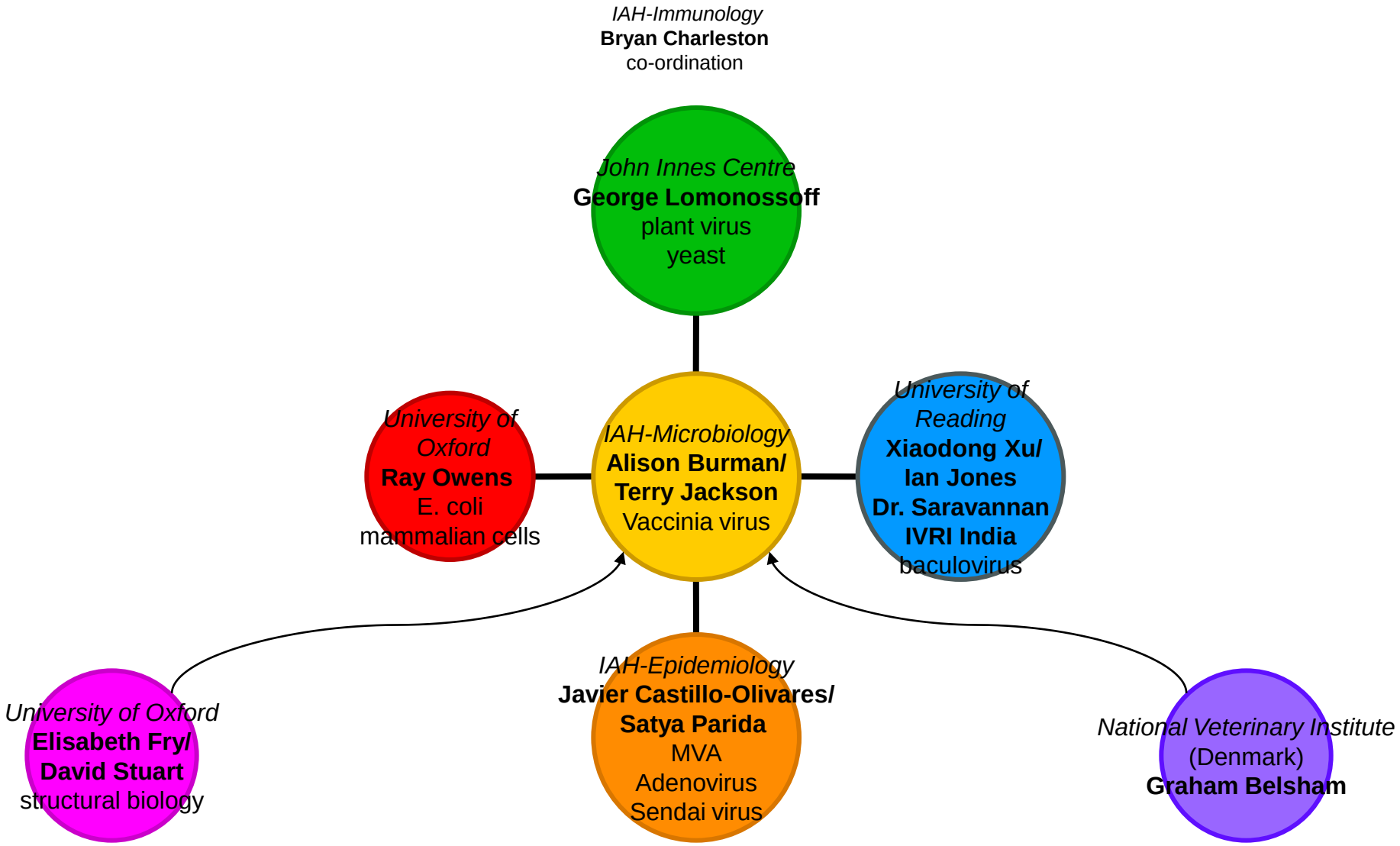
The way forward

Improve understanding of immune response
Target antigen to antigen presenting cells
Stabilise vaccine antigen

Dendritic cell targeting of FMDV antigen can be improved



Consortium


IAH-Immunology
Bryan Charleston
co-ordination
John Innes Centre
George Lomonossoff
plant virus
yeast
University of Oxford
Ray Owens
E. coli
mammalian cells
IAH-Microbiology
Alison Burman/
Terry Jackson
Vaccinia virus
University of Reading
Xiaodong Xu/
Ian Jones
Dr. Saravannan
IVRI India
baculovirus
University of Oxford
Elisabeth Fry/
David Stuart
structural biology
IAH-Epidemiology
Javier Castillo-Olivares/
Satya Parida
MVA
Adenovirus
Sendai virus
National Veterinary Institute
(Denmark)
Graham Belsham

Sequences likely to enhance expression in mammalian cells

- At the 5’ end

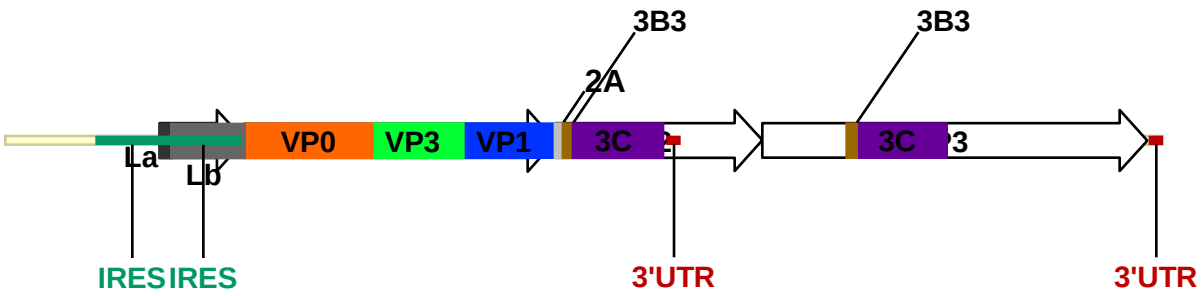
  IRES → not all the T7 transcripts get capped during co-expression of two recombinant vaccinia viruses

  + “La”→ 75% initiation downstream of the FMDV IRES occurs at the second AUG

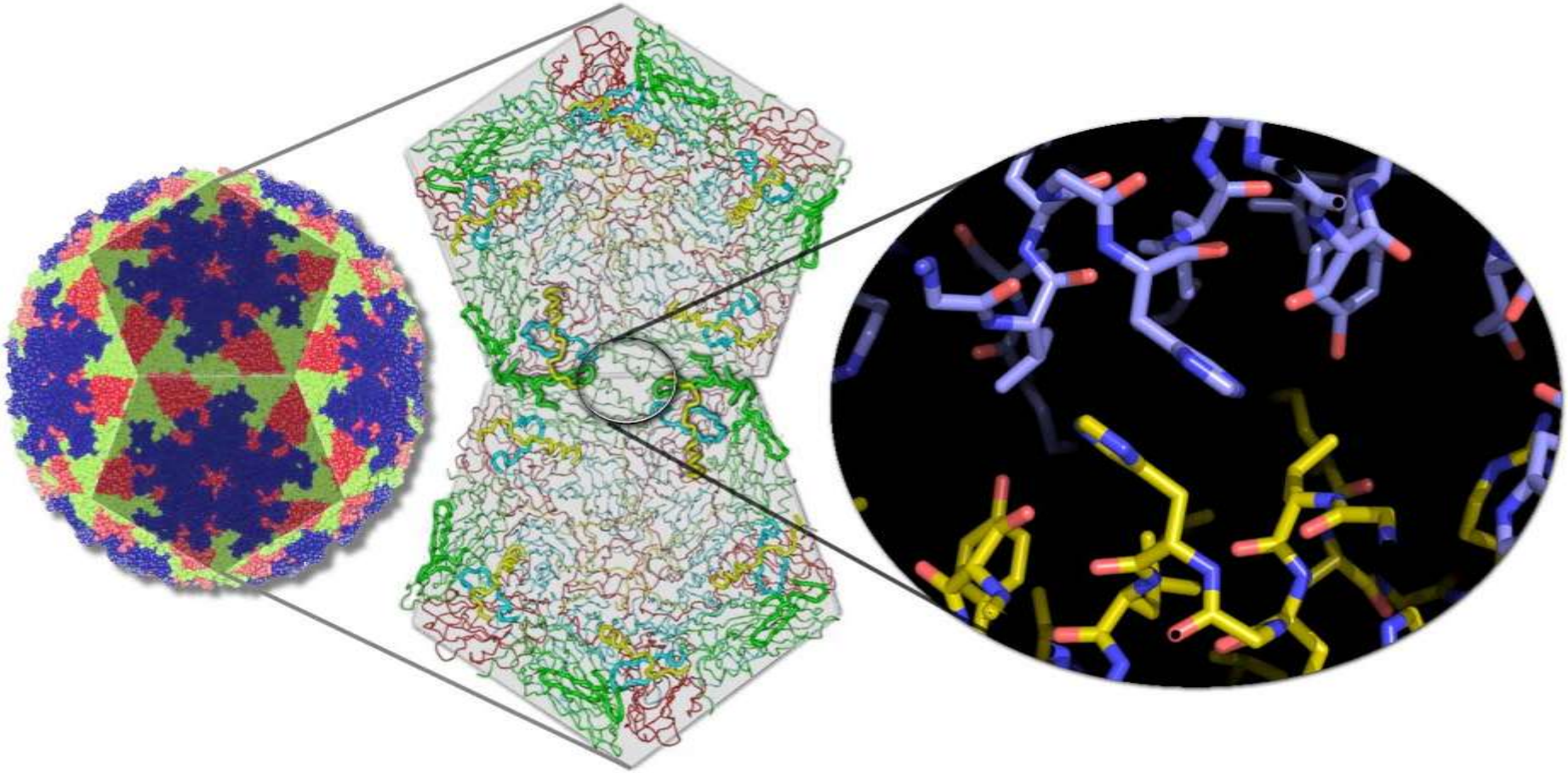
- At the 3’ end

  3’UTR

  + poly (A) tail → separately enhance IRES-mediated translation

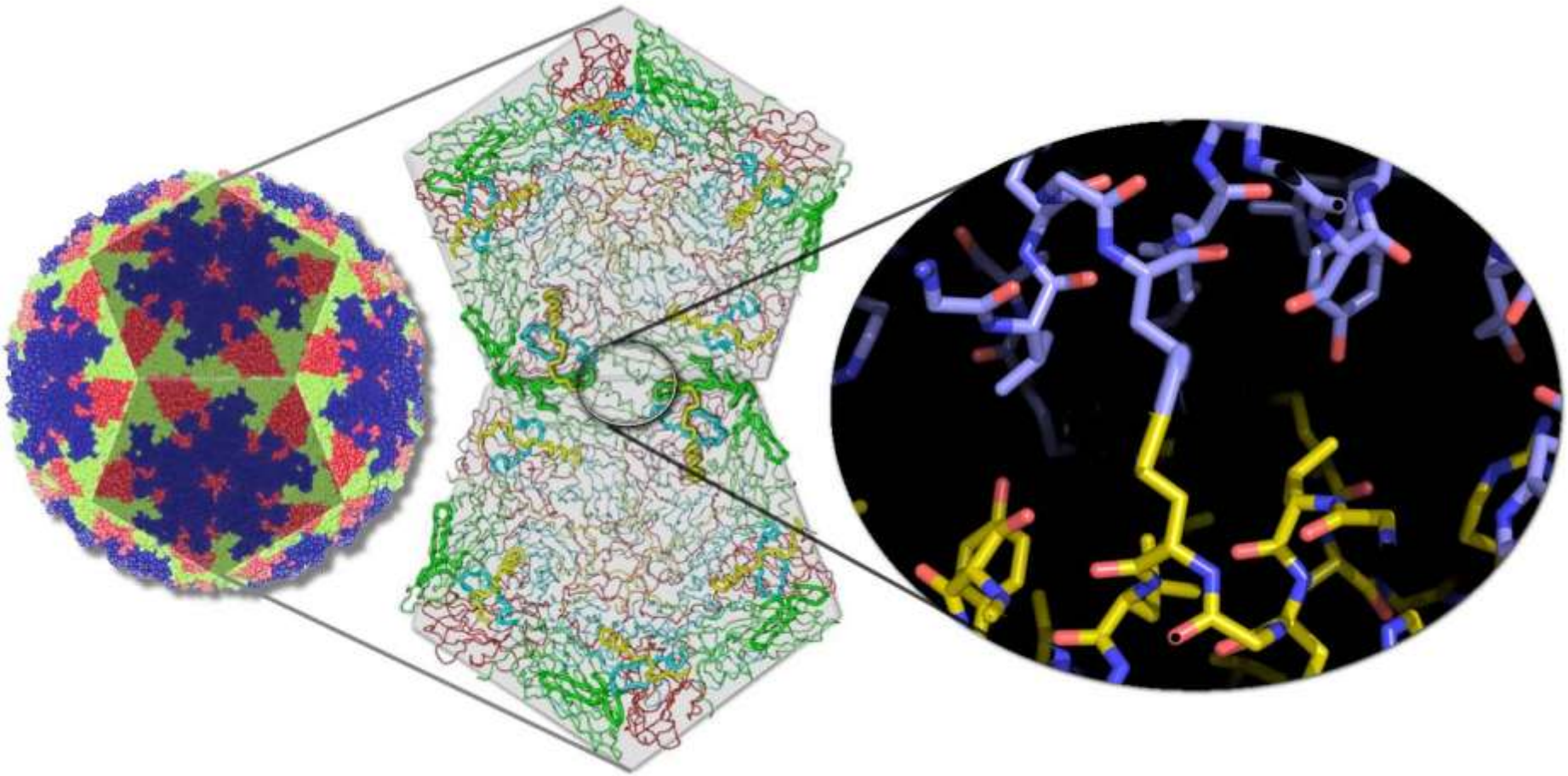


Structure-based stabilisation of FMDV capsids



Proof of principle that an engineered mutation (his to cys) is consistent with capsid assembly.
Similar approaches can be used for infectious copies.

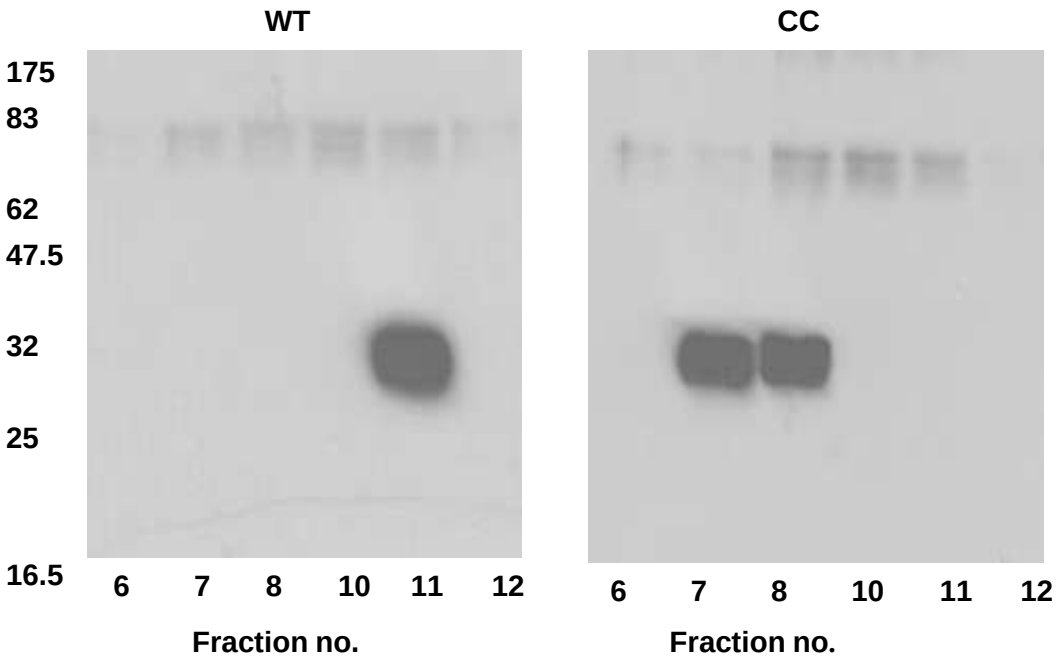
Structure-based stabilisation of FMDV capsids



Proof of principle that an engineered mutation (his to cys) is consistent with capsid assembly.
Similar approaches can be used for infectious copies.

Covalent Cage Particle Characterisation

CC and WT empties were treated for 2h at 56ºC (or for 30min at pH5), then subjected to sucrose density gradients.



Assembled empty particles seen in CC fractions only.

Improved stability

- Enhanced storage characteristics of formulated products

-Enhanced duration of immunity when combined with depot delivery system

-Improved T cell responses as a consequence of enhanced antigen presentation

Persistence of FMDV antigen

- maintaining protective antibody responses

MLN 38DPCI

LZ

DZ

80 µm

FMDV D46 DAPI

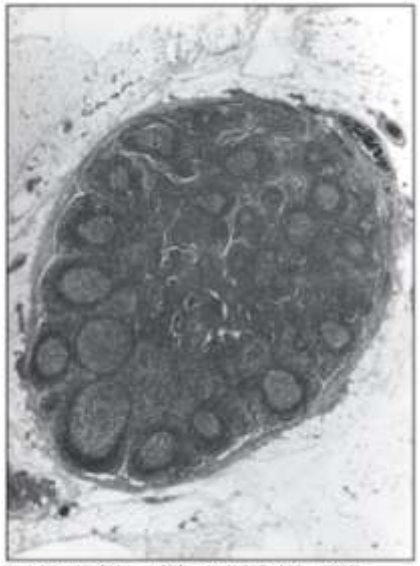
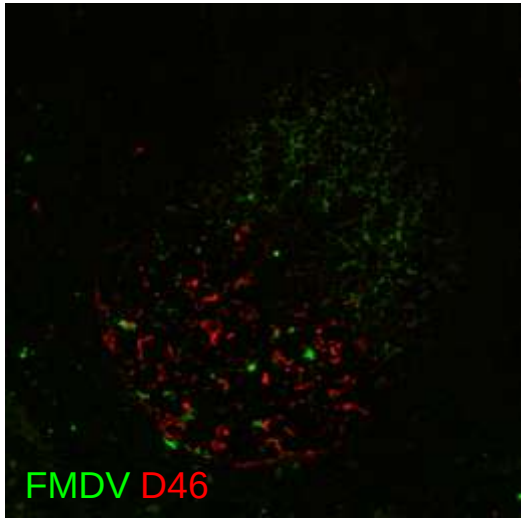
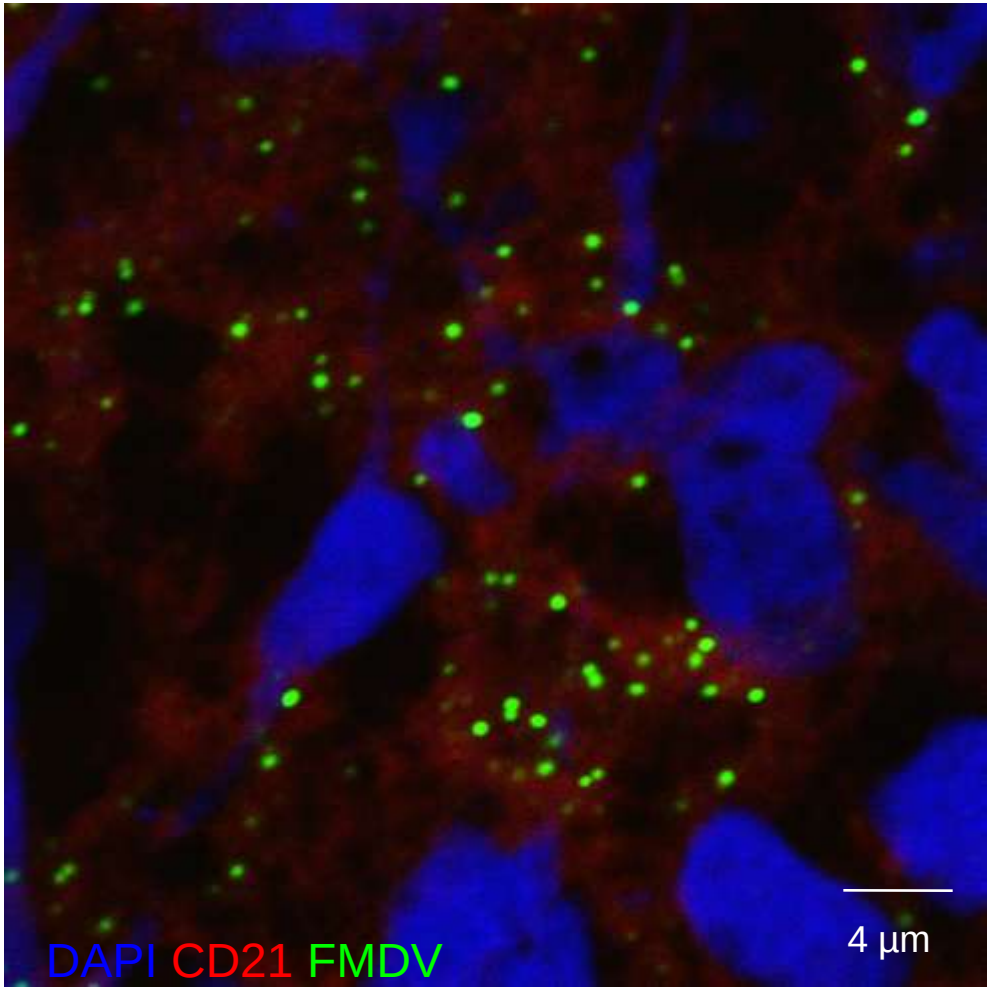
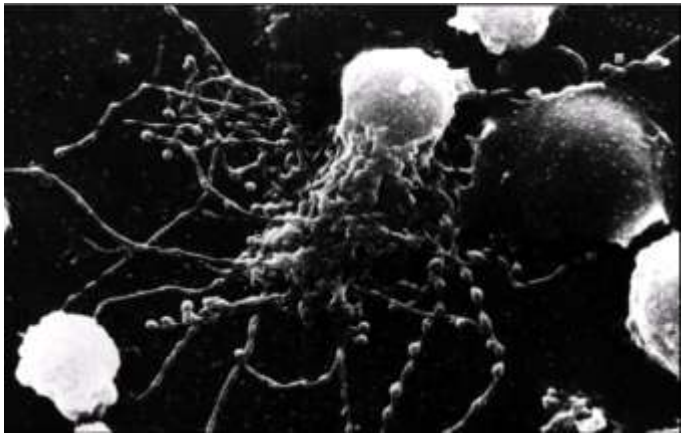


Figure 1-8 part 2 of 2 Immunobiology, 6/e. © Garland Science 2005





No expression of non-structural proteins:
-Non-replicating
-Extracellular



Collaboration with OVI in southern Africa

Hypothesis

In the major wildlife reservoir of FDMV in Sub-Saharan Africa, the buffalo, depots of viable, non-replicating viruses seed other tissue that results in the production of transmissible virus.

Primary objectives

1: Determine whether FMDV capsid and genome are present in buffalo lymphoid tissue.
2: Determine whether secondary sites of FMDV localisation or replication are detectable in buffalo.
3: Determine whether infectious virus can be isolated from buffalo lymphoid tissue or epithelium after the resolution of clinical signs.
4: Compare the genetic complexity of viral depots in buffalo tissue with virus present in oropharyngeal samples collected by probang.
5: Develop minimally invasive sampling techniques for lymphoid tissue from buffalo to aid surveillance.

Global Foot-and-Mouth Disease
Research Alliance