icrad
International coordination of research on infectious animal diseases

THE Pirbright INSTITUTE

Project NEOVACC : Novel strategies to enhance vaccine immunity in neonatal livestock

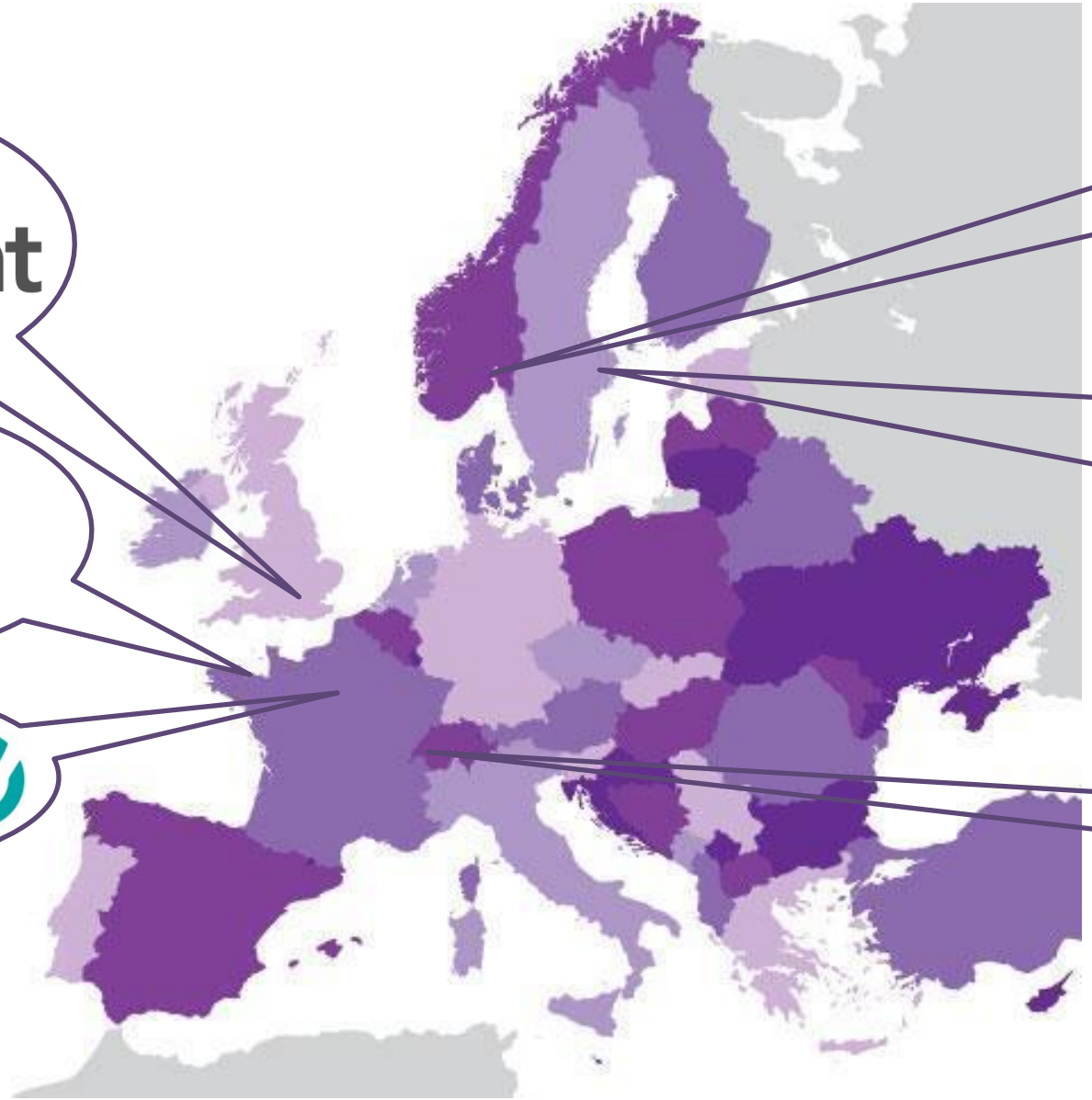
Prof Simon P. Graham

Project Coordinator

ICRAD Initial Grant Holders' Meeting
27th May 2021

Biotechnology and Biological Sciences Research Council
Pirbright receives strategic funding from BBSRC UKRI

NEOVACC partners



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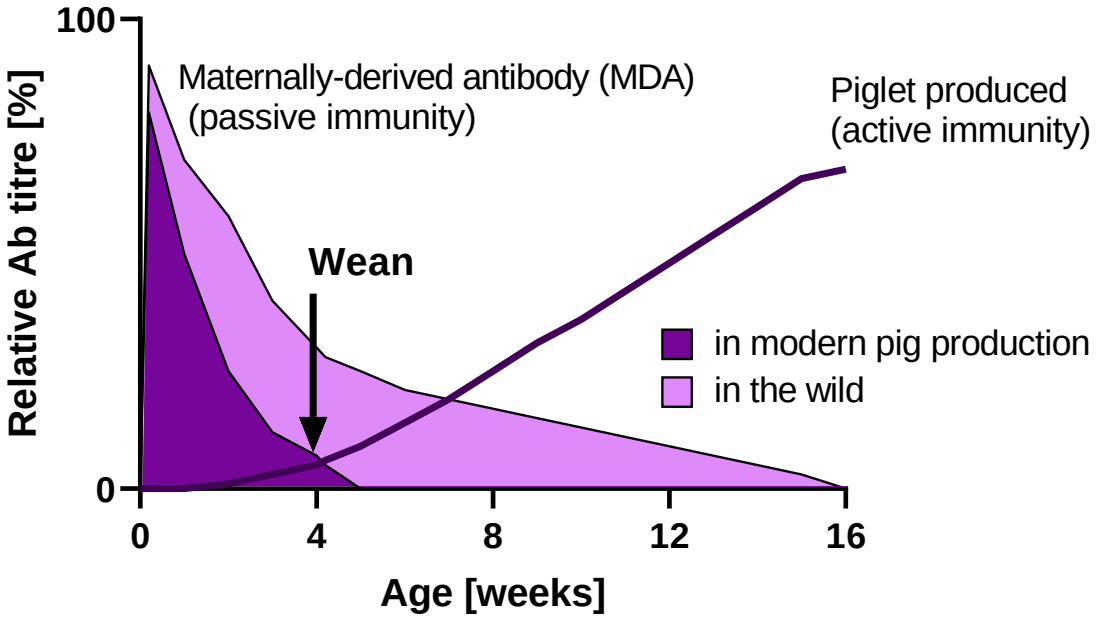
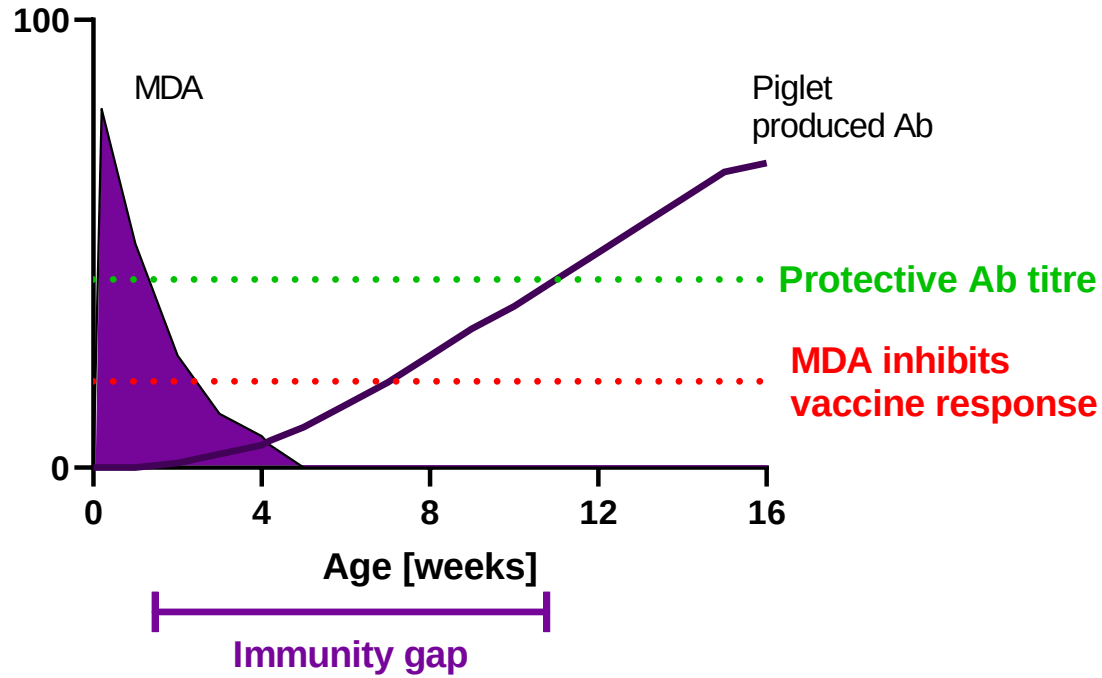
NEOVACC introduction

ICRAD Research area 2: Generic technology platforms for producing novel and/or improved vaccines

Novel strategies to enhance vaccine immunity in neonatal livestock - closing the 'immunity gap'

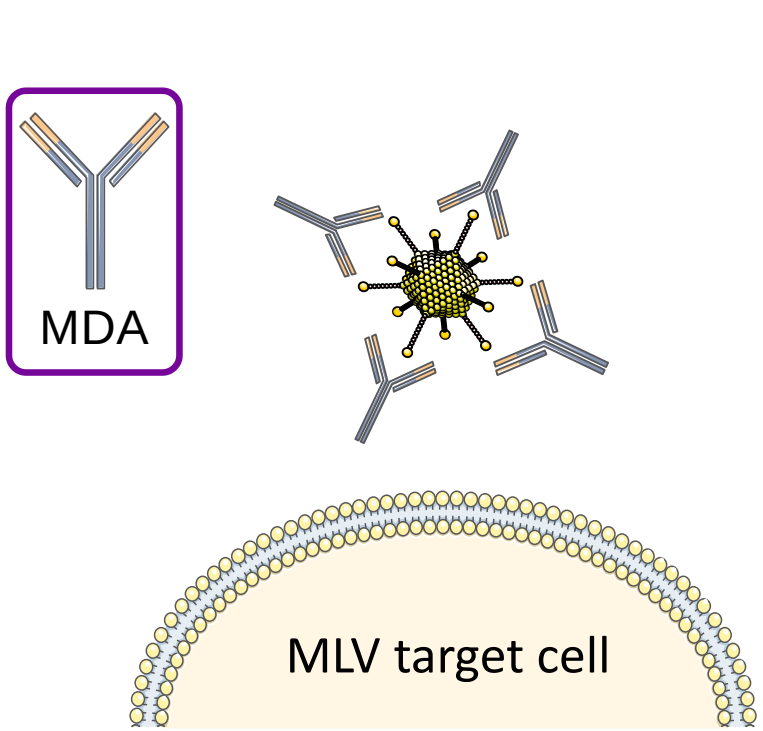
Maternal immunity and the 'immunity gap'



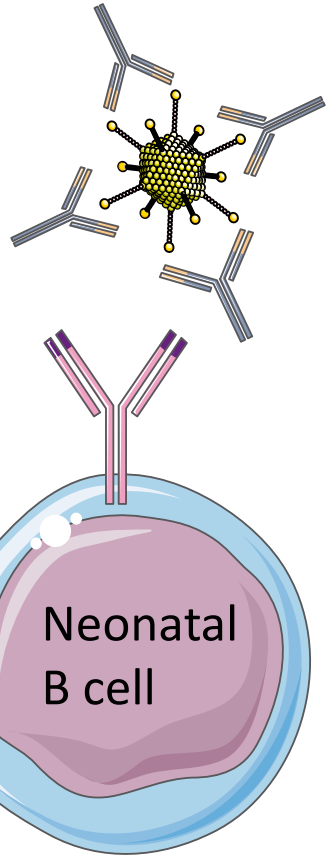


NEOVACC introduction

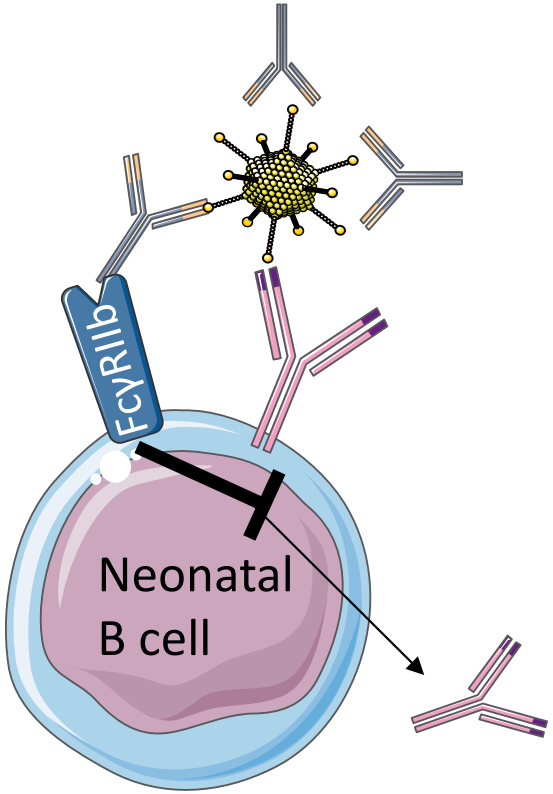
Interference of vaccine responses by MDA:



1. Neutralisation of live vaccines



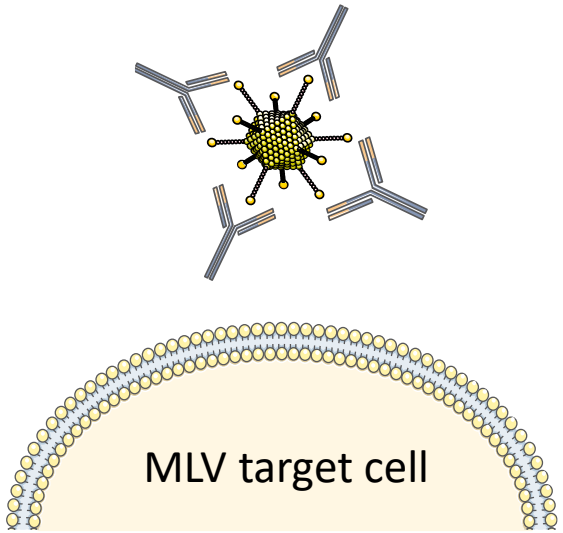
2. Epitope masking

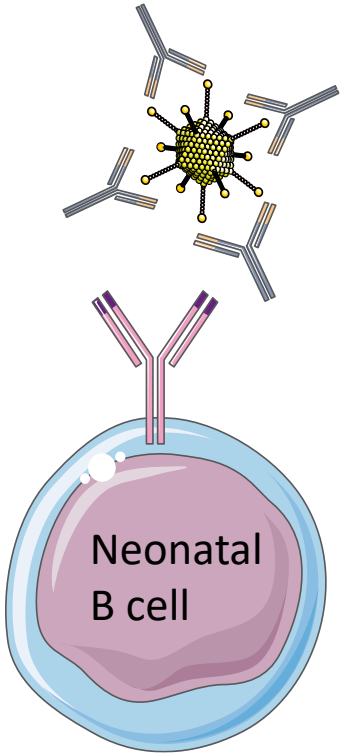


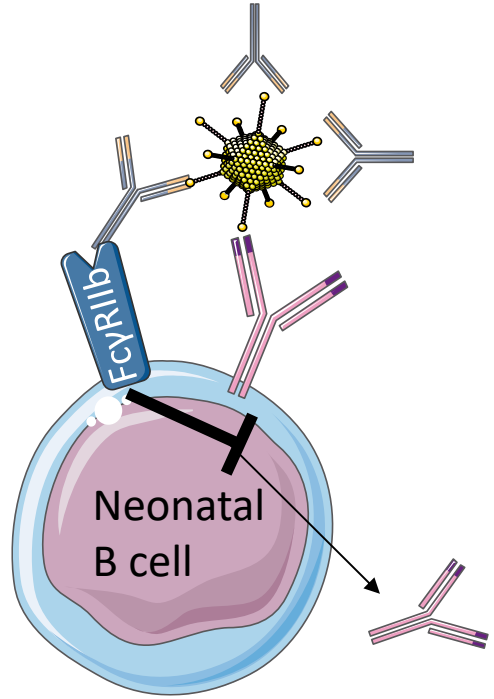
3. Negative regulation by FcγRIIb

NEOVACC aims

Strategies to combat interference of MDA on vaccine responses:







1. Neutralisation of live vaccines
 - Genetic engineering to enhance live vaccine immunogenicity

2. Epitope masking
- Designing immunogens to exploit differences in Ab repertoires between adults and neonates

3. Negative regulation by FcgRIIb
- A DNA vaccine approach to counteract MDA interference on neonatal B cells

NEOVACC disease targets/models

Bovine respiratory syncytial virus (BRSV)

Major cause of lung disease in calves
Key pathogen in the bovine respiratory disease complex
Major economic losses (EU – 580M € pa)
Impaired animal welfare
Increased usage of antibiotics

Multivalent vaccines against BRD include inactivated & live-attenuated BRSV but are moderately effective

- Interference with MDA
- Short duration of immunity
- Risk of disease exacerbation

Structural vaccinology applied to develop an effective subunit vaccine – BRSV fusion protein stabilized in the prefusion conformation (pre-F)

Porcine reproductive and respiratory syndrome virus (PRRSV)

Major cause of lung disease in piglets
Key pathogen in the porcine respiratory disease complex
Major economic losses (EU – 1,5B € pa)
Impaired animal welfare
Increased usage of antibiotics

Inactivated & live-attenuated PRRSV but are moderately effective

- Inactivated vaccine ineffective in naïve piglets
- MLV are partially effective, restricted breadth of protection and drive virus escape
- MDA impairs the immune response to MLV reducing efficacy

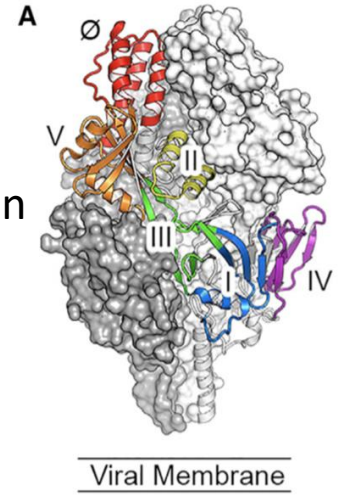
Next generation vaccines (subunits and vectored vaccines) struggle to provide effective immunity
DNA-MLV prime-boost strategy enhanced the antibody response and broadened the T-cell response

WP1: Designing BSRV immunogens to exploit differences in antibody repertoires between adult and neonatal cattle

Background/rationale:

- Calves mount protective immune responses when immunised with BRSV pre-F, despite the presence of MDA
- Human infant antibody responses to RSV F differ substantially from those of healthy adults. Primarily targeting antigenic sites I and III - not dominant in adult responses
- Established TopoBuilder - a protein design algorithm to engineer immunogens displaying conformational epitopes - validated with RSV epitopes
- Take advantage of the discrete differences between the maternal and neonatal antibody repertoires and in silico designed BRSV F epitopes as an optimised vaccine strategy for newborn calves - prevent epitope masking & inhibitory effects of MDA

Antigenic sites on RSV Pre-F

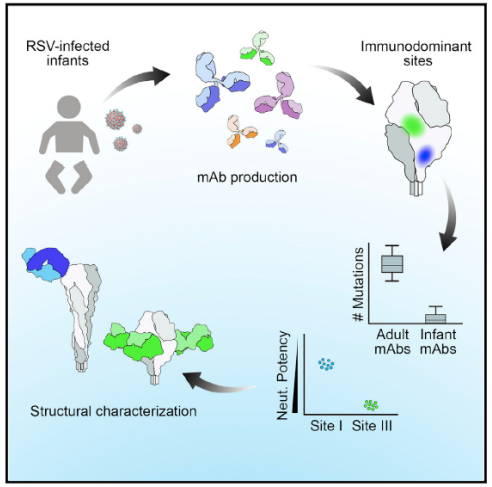


Article

Immunity

Infants Infected with Respiratory Syncytial Virus Generate Potent Neutralizing Antibodies that Lack Somatic Hypermutation

Graphical Abstract



Authors

Eileen Goodwin, Morgan S.A. Gilman, Daniel Wrapp, ..., Barney S. Graham, Jason S. McLellan, Laura M. Walker

Correspondence

jason.s.mclellan@dartmouth.edu (J.S.M.), laura.walker@adimab.com (L.M.W.)

In Brief

An increased understanding of infant antibody responses to RSV infection would greatly facilitate vaccine development. Goodwin et al. isolate and structurally characterize antibodies from RSV-infected infants and identify potent neutralizing antibodies that lack somatic hypermutation. The results provide a framework for the rational design of age-specific RSV vaccines.

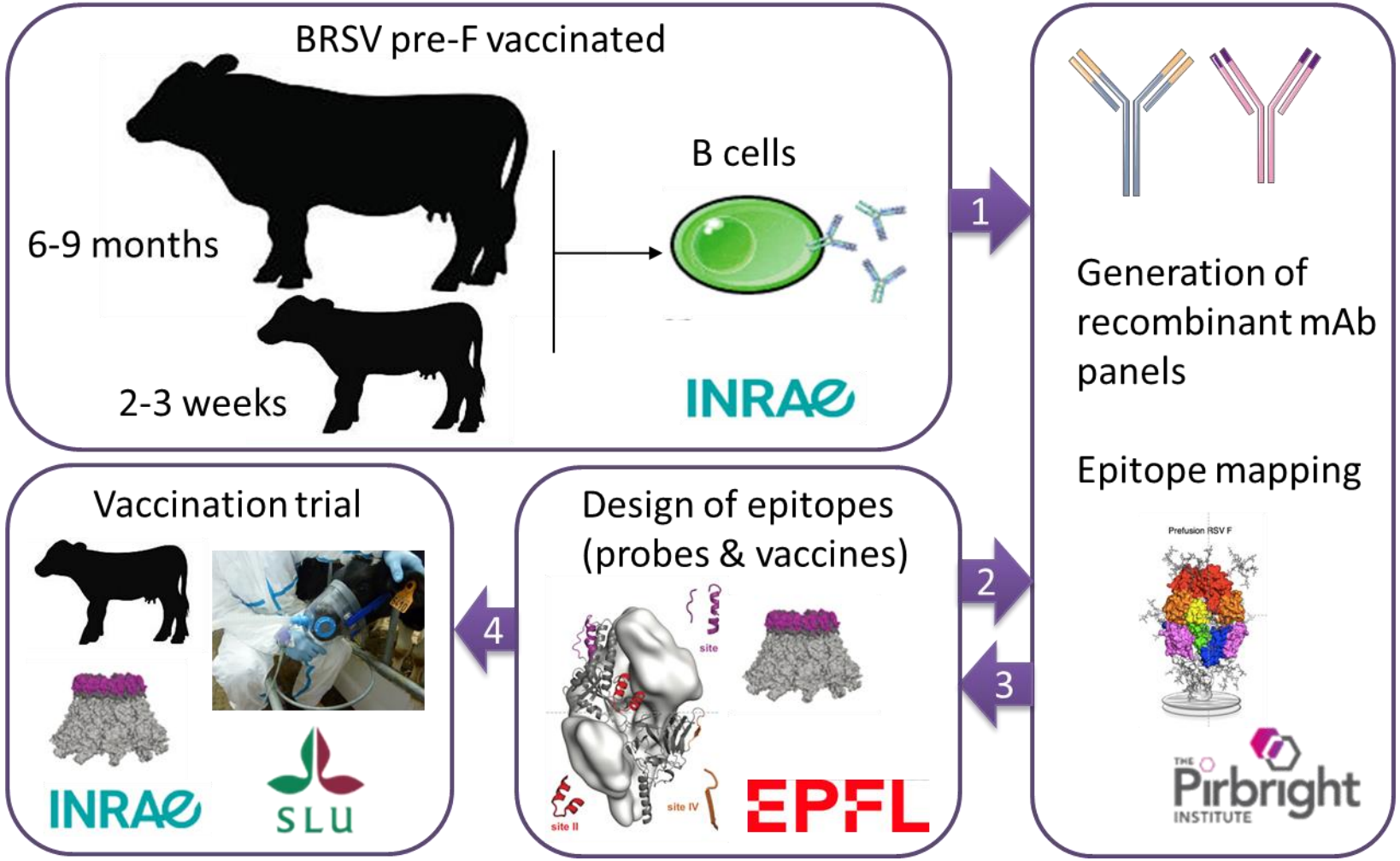
WP1: Designing BSRV immunogens to exploit differences in antibody repertoires between adult and neonatal cattle

Approach:

1. Identify BRSV-preF neutralising Ab epitopes that differentiate the adult versus neonatal antibody repertoires.

2. Design in silico scaffold epitopes from the BRSV fusion protein with optimal antigenicity for bovine neonate or young adult cattle to increase BRSV vaccine efficacy.

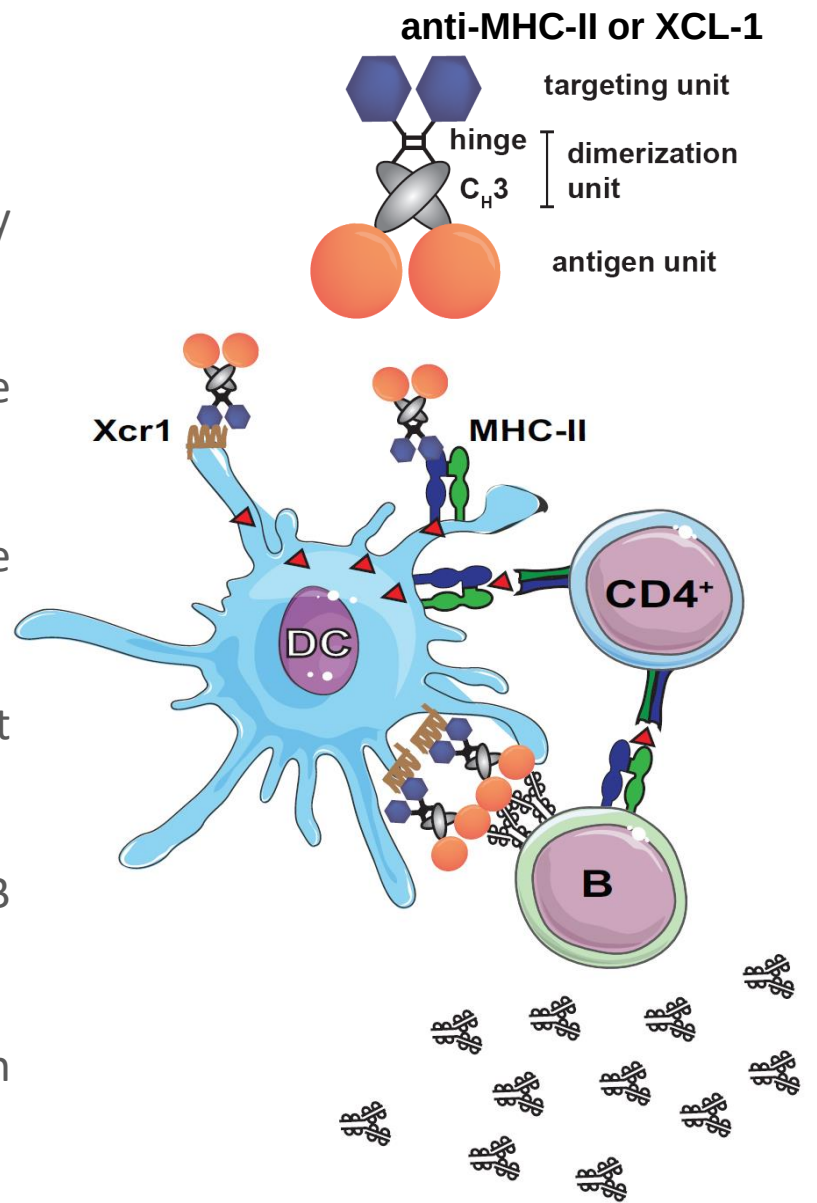
3. Validate the new vaccine candidates (as scaffold epitopes) for protection against an experimental BRSV challenge in calves with MDA.



WP2: A DNA vaccine-based approach against PRRSV to counteract MDA interference

Background/rationale:

- DNA vaccines induce significant cell-mediated responses and evade the inhibitory effect of MDA on Ab responses
- DNA vaccines may promote the formation of DC/T/B cell synapses that alleviate the negative impact of immune complex formation on FcγRIIb signalling
- Fusing antigen to chemokines or antibodies specific for DC receptors can enhance antibody responses in pigs
- After DNA vaccination, dimeric fusion vaccines are secreted and bind to target cells: XCL1 → XCR1 on cDC1s, anti-MHC-II → DCs & other APCs.
- Targeting DCs may enhance presentation of antigen to CD4 T cells and improve B cell help.
- Fusion vaccines may remain on the surface of the DCs and assist in the formation of APC/B cell synapses.



WP2: A DNA vaccine-based approach against PRRSV to counteract MDA interference

Aims:

- Test whether a targeted DNA prime / MLV boost vaccination enhances cell mediated and Ab responses in MDA+ piglets
- Assess if a broad targeting approach (anti-MHC-II) is more beneficial than a narrow targeting approach (XCL1) in preventing inhibition by MDA.
- To investigate in vitro whether targeting of antigens to DCs favours DC/T/B cell crosstalk that escapes the negative effects of MDA.

Approach:

- *In vivo* evaluation of DNA vaccines: PRRSV GP5, NSP5, M and N fused to XCL1, anti-MHC-II scFv or delivered as non-targeted antigens. Delivered to MDA+ piglets prior to MLV boost.

- *In vitro* assessment of DC-targeted antigens to counteract MDA effects on B-cell responses.

48 MDA+ piglets		
D3 Prime	**D42 Boost**	**D70 Challenge**
DNA untargeted	MLV	√
DNA-XCL-1	MLV	√
DNA-MHC-II	MLV	√
MLV	MLV	√
-	MLV	√
-	-	√

WP3: Engineering immune checkpoint inhibitors to enhance neonatal responses to vaccination

Background/rationale:

Immune checkpoint molecules are natural regulators of T cell responses. Engagement of immune checkpoint receptors e.g. PD-1 and CTLA-4 with ligands switches T cells 'OFF'

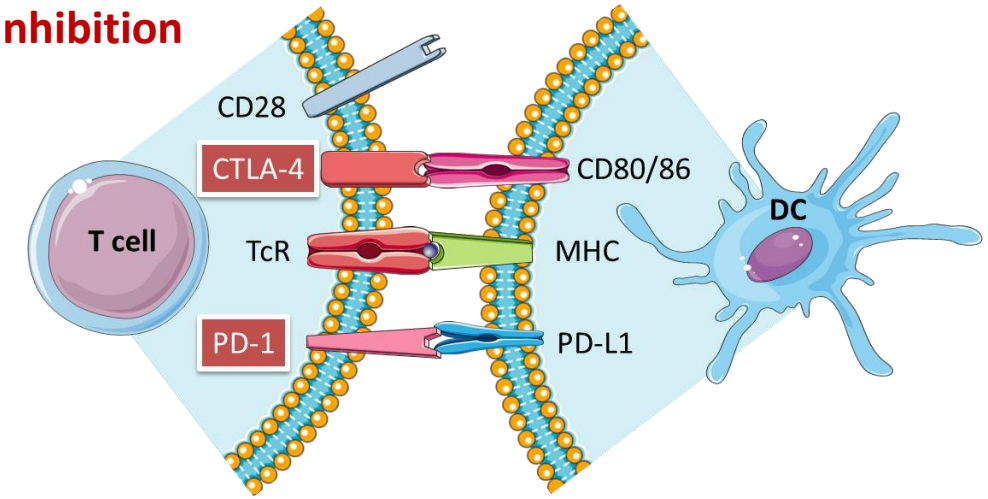
Immune checkpoint inhibitors (ICI) e.g. monoclonal antibodies which bind PD-1/CTLA-4, switch T cells back 'ON'

ICI are promising cancer immunotherapeutics and emerging as a novel class of adjuvant

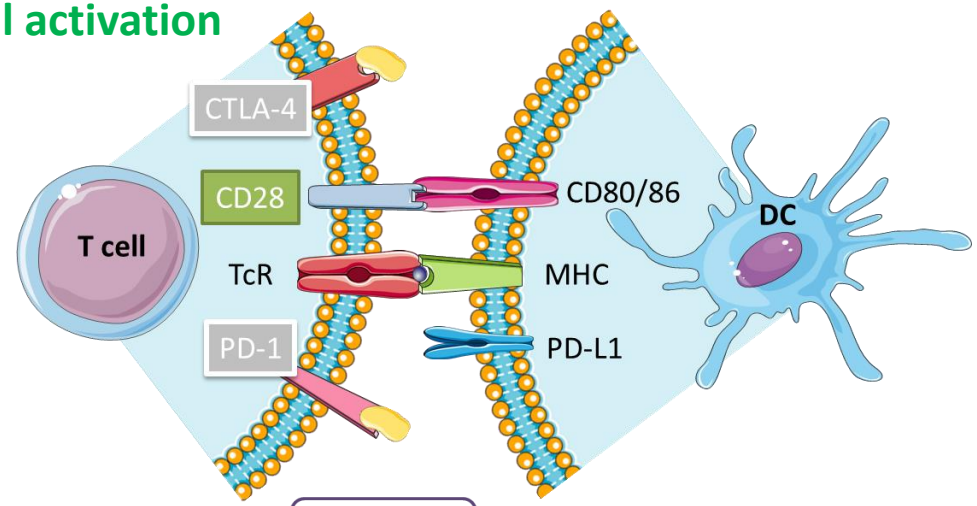
Microtides LD01 & LD10 are potent peptide-based PD-1 & CTLA-4 antagonists. Demonstrated to enhance immune responses to viral vectored and live attenuated malaria vaccines

PRRS MLV are weakly immunogenic, and evidence suggests they retain the ability to modulate immunoregulatory pathways

T cell inhibition



Immune checkpoint inhibition & T cell activation



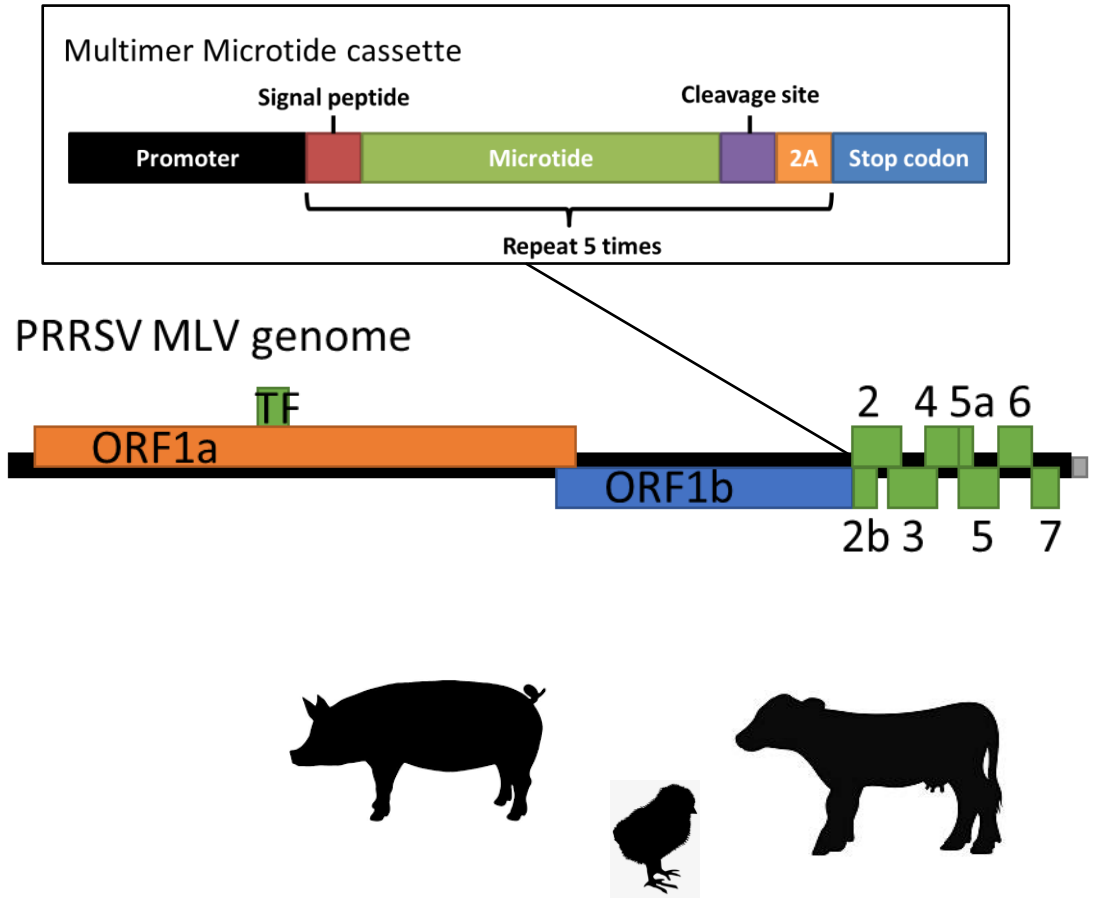
WP3: Engineering immune checkpoint inhibitors to enhance neonatal responses to vaccination

Aim:

To assess whether PRRSV MLV genetically engineered to express Microtide ICIs confer enhanced protection of MDA+ piglets

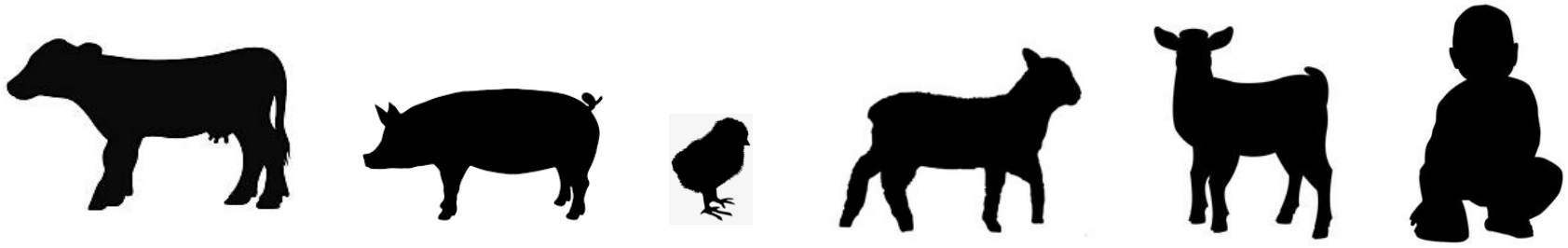
Objectives:

1. Construct and characterise recombinant PRRSV-1 MLV expressing Microtide ICIs *in vitro*
2. Evaluate the safety, immunogenicity and efficacy of recombinant PRRSV MLV expressing Microtide ICIs
3. Evaluate the biological activity of Microtide ICIs on bovine and galline T cells *in vitro*



Expected impact

- Proof of concept for innovative vaccines for major viral diseases of cattle and pigs
- Vaccines that would close the ‘immunity gap’ and protect animals during a vulnerable period
- Approaches may be exploited in the context of other pathogens, livestock species and humans



Acknowledgements

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