STAR-IDAZ
International Research
Consortium on Animal Health

Roadmaps for the development of candidate vaccines for Brucella, PRRSV and bTB

SIRCAH Deliverable 3.2

Version 1, 31/03/2018

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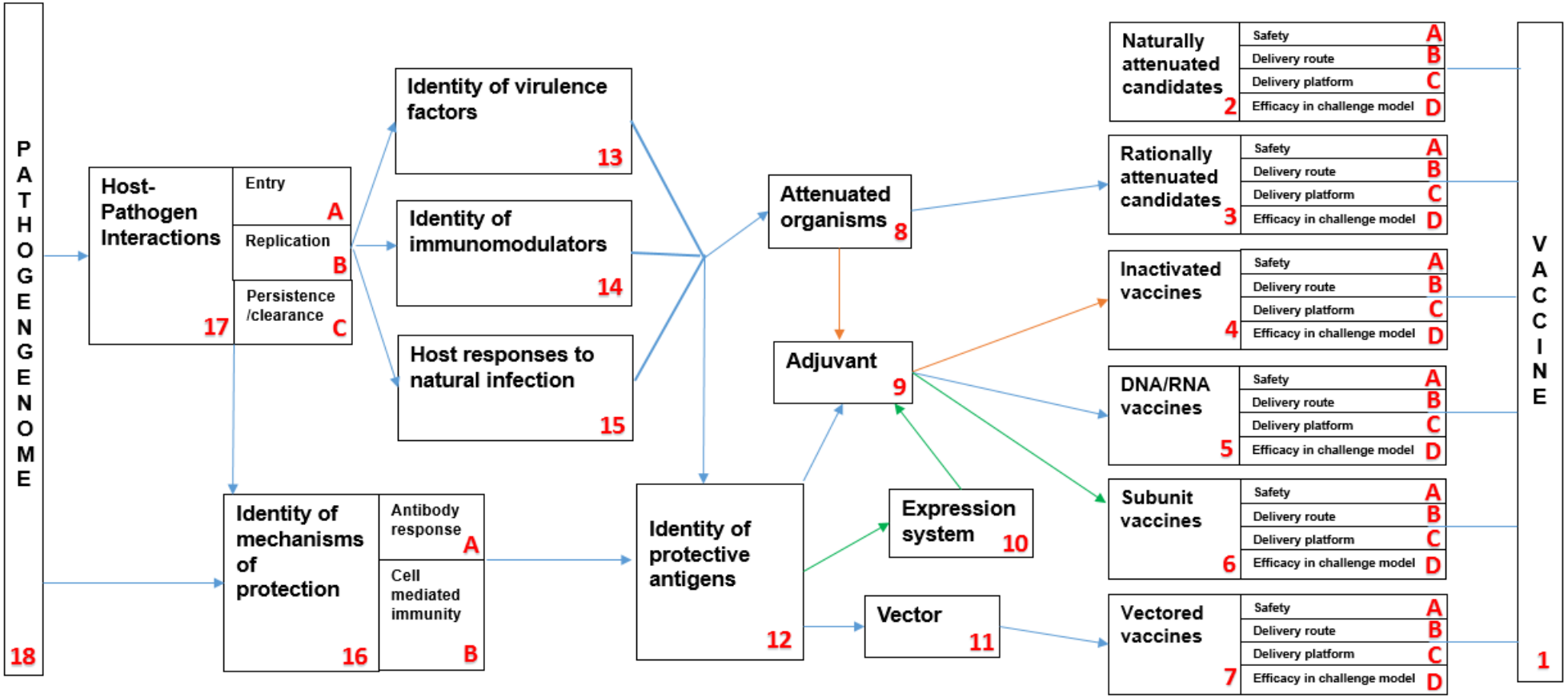
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Roadmap for development of a candidate vaccine for PRRSV

Version 1, 31/03/2018

Lead Summary 1

Title:	An improved multivalent PRRSV vaccine preventing disease, virus transmission and carrier state in vaccinated animals

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Protection against disease caused by the various virus strains.
Sterile immunity
Prevent vaccine virus contributing to evolution of field isolates
Virus eradication from a herd

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Cross-protection against the various isolates
Attenuated live viruses can contribute to virus evolution
Generation of both a CTC and VN response
The dominant immunogens may not be protective

Solution Routes

What approaches could/should be taken to address the research question?

Establish protection levels with various candidate vaccine options, including priming with one vaccine and boosting with a different vaccine.
Establish if pig genetics influences responses
Incorporate the candidate vaccine in a vaccine platform covering a number of diseases
The development of farm strain-specific vaccines (autologous vaccines)

Dependencies

What else needs to be done before we can solve this need?

Development of cross protective/multivalent killed vaccine
Development of a cross protective/multivalent vectored vaccine
Development of a subunit vaccine
Development of an attenuated vaccine that doesn't persist or is excreted

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 3

Title:	Development of an attenuated vaccine that doesn't persist or is excreted

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Replicating organisms are likely to give the most appropriate immune response but wild-type virus manipulates the host response. The aim is to reduce the virulence of the organism so that the vaccinated animal can mount a protective immune response

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

The generation of GM organisms that are viable but lack virulence and non-protective immune-dominant antigens.
Identification of strains that give the greatest cross protection.
That vaccination prevents excretion of the organism – both the vaccine strain and wild type virus or any combination of the two that may have been generated

Solution Routes

What approaches could/should be taken to address the research question?

Monitoring the immune response following immunisation with the various candidates.
Challenge experiments with the various vaccine candidates, including challenge with other strains
Identity of cell lines that allow higher production of PRRSV

Dependencies

What else needs to be done before we can solve this need?

The generation of stable genetically modified organisms
Identity of virulence factors in PRRSV
Identity of immunomodulators in PRRSV

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 4

Title:	Development of cross protective/multivalent killed vaccine

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of an effective killed virus vaccine that gives broad cross-protection but doesn't contribute to virus evolution.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Having it multivalent
Having the protective response involving both VN Abs and CTC
Initial Ab response following natural infection isn't protective

Solution Routes

What approaches could/should be taken to address the research question?

Generation of a range of recombinant viruses expressing protective Antigens from a range of viruses but **lacking** the dominant Antigen to which the initial non protective Ab response is generated.
Monitoring the immune response following immunisation with the various candidates.
Challenge experiments with the various vaccine candidates.
If a multivalent vaccine isn't possible then a system for rapid development of autologous vaccines will be needed.

Dependencies

What else needs to be done before we can solve this need?

Identifying a combination of antigens for expression by a GM strain of the virus **or** a common single protective Ag to which immune responses are normally suppressed
The availability of suitable adjuvants to stimulate strong CTC and VN-Ab responses.

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 6

Title:	Development of a cross protective/multivalent subunit vaccine

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of an effective subunit vaccine that gives broad cross-protective sterile immunity but doesn't contribute to virus evolution.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Having it multivalent
Having the protective response involving both VN-Abs and CTC

Solution Routes

What approaches could/should be taken to address the research question?

Establishing that there isn't interference between the various antigens
Monitoring the immune response following immunisation with the various combinations of candidate immunogens.
Challenge experiments with the various vaccine candidates.
If a multivalent vaccine isn't possible then strain specific autologous vaccines based on recognised antigen combinations will be needed.
Production of virus-like particles containing all the desired surface proteins of PRRSV

Dependencies

What else needs to be done before we can solve this need?

Identifying a combination of antigens for expression by a suitable expression vector **or** a common single Ag to which immune responses are normally suppressed
The availability of suitable adjuvants to stimulate strong CTC and VNAb responses
Identifying expression systems that give correct Antigen conformation

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 7

Title:	Development of a cross protective/multivalent vectored PRRSV vaccine

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The development of an effective vaccine that gives broad cross-protection but doesn't contribute to virus evolution.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Generating a strong protective immune response with CTCs and VN Abs

Preventing the development of immune responses to the vector

Solution Routes

What approaches could/should be taken to address the research question?

Monitoring the immune response following immunisation with the various candidates involving single/combination of antigens.

Challenge experiments with the various vaccine candidates.

Development of vaccine platforms

Identify most appropriate route of administration (parenteral/oral/nasal)

Dependencies

What else needs to be done before we can solve this need?

Identifying a combination of antigens for expression by a vector or a common single Ag to which immune responses are normally suppressed

Identifying suitable vector

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 8

Title:	The generation of rationally attenuated genetically modified PRRSV

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To generate organisms that are less virulent in terms of pathological changes that they cause and/or their ability to modulate the host's immune responses – rationally attenuated vaccine

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

That the organisms are stable and can be produced in cell culture
That they still generate a protective response

Solution Routes

What approaches could/should be taken to address the research question?

Generation of infectious cDNA clones
Generation and characterisation of a range of rationally attenuated organisms (using codon pair deoptimisation)
Immune response to the attenuated organisms

Dependencies

What else needs to be done before we can solve this need?

Identity of Virulence factors and their genes
Identity of immunomodulators

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 9

Title:	Identifying suitable delivery systems for subunit and inactivated whole virus vaccine candidates

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Generate an optimal immune response to the various vaccine candidates resulting in sterile immunity to wild type virus

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Generating both a strong VN Ab and a CTC response

Solution Routes

What approaches could/should be taken to address the research question?

Immune response to antigens delivered on Nanoparticles
Immune response following inclusion of various adjuvants with the candidate vaccines

Dependencies

What else needs to be done before we can solve this need?

Identity of protective antigens

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 11

Title:	Identifying suitable vector for the expression/delivery of protective PRRSV Antigens

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The generation of protective responses without the risk of the recombination between an attenuated strain and wild strains

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

The expression of the protective Antigens by a replicating organism with the development of VN-Abs and CTC responses.
Creating stable genetically modified organisms expressing the desired PRRSV antigens.
Identifying the Ag combination to give widest protection against the various field isolates

Solution Routes

What approaches could/should be taken to address the research question?

Generation of genetically modifies organisms (viruses or bacteria) expressing the protective antigens of different PRRSV strains
Incorporation of molecular adjuvants (expressing CD40 ligand)

Dependencies

What else needs to be done before we can solve this need?

Identity of the most appropriate antigens

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Adeno (canine adeno virus) virus with GP5 epitope and M proteins
PCV2
Alphavirus
Attenuated pseudo-rabies virus
Transmissible Gastroenteritis virus
BCG
Replication deficient adenoviruses
Poxviral vectors

Lead Summary 12

Title:	Identity of protective Antigens

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

The identity of the virus components (epitopes) that the host needs to respond to to **prevent** and **clear** infection

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

The dominant immunogens may not be protective so a range of possible antigens will need to be considered.
There is a lot of antigenic variability and genetic drift from the high mutation rate of the virus so identifying the most stable/conserved antigens is important

Solution Routes

What approaches could/should be taken to address the research question?

The identity of the antigens that the host is generating Abs to and their role in protection (preventing and clearing infection).
To identify the antigens that are responsible for protective cellular responses.
Identifying possible protective antigens in the virus genome, their expression and trial in challenge experiments

Dependencies

What else needs to be done before we can solve this need?

Identity of protective mechanisms operating in immune hosts – the role of neutralising Abs and CTCs.
The genome sequence of various virus isolates

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

GP5
GP3; NSP 5; M protein

Lead Summary 13

Title:	To establish the identity of the virulence factors in PRRSV that contribute to disease pathology

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Identifying and removal of the factors contributing to pathological changes are essential for generating rationally attenuated vaccines

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes

What approaches could/should be taken to address the research question?

Swapping of suspected virulence genes between virulent and attenuated viruses using infectious cDNA clones
Generation of a range of knock-out viruses and their use in experimental infections to establish the impact of the changes on virulence

Dependencies

What else needs to be done before we can solve this need?

Improved understanding of virus macrophage interaction – viral and macrophage gene expression in different in vivo environments (macrophages from naïve and immune hosts)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 14

Title:	To establish the identity of the immunomodulatory factors/stealth mechanisms in PRRSV

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

PRRSV attempts to modulate the host's immune responses so that it can survive and replicate.
The early Ab response isn't protective and VN-Abs don't appear until 6 weeks into infection
Identifying and removal of the factors contributing to the virus stealth mechanisms could contribute to the generation of improved attenuated vaccine candidates

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes

What approaches could/should be taken to address the research question?

Generation of a range of knock-out viruses where the genes for various immunomodulatory factors or other stealth mechanisms have been removed and their use in experimental infections.
Modulation of innate immune responses

Dependencies

What else needs to be done before we can solve this need?

Improved understanding of virus-macrophage interaction – viral and macrophage gene expression in different in vivo environments (macrophages from naïve and immune hosts)

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Dysregulation of NK cell function/suppression of NK Cell activity
Dysregulation of IFNα production (nsp 1, 2, 4, 11)

Lead Summary 16

Title:	To identify protective mechanisms in PRRSV infected animals

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

Identify the mechanisms operating in immune animals, establishing the role of Abs and CMI in **preventing** and **clearing** infection.

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

Solution Routes

What approaches could/should be taken to address the research question?

To identify the role of Ab and CMI in providing protection against infection – passive transfer experiments
To establish the role of the various cell types and cytokine responses in clearing infection
Establishing the identity of the leukocytes that are effective in eliminating infected mø

Dependencies

What else needs to be done before we can solve this need?

An improved understanding of host virus interaction at the level of the infected cells.
The genome sequence of various PRRSV isolates

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

NSP5 and M protein cytotoxic Tcell responses

Lead Summary 17

Title:	Host Pathogen interaction in PRRSV infection

Research Question

What are we trying to achieve and why? What is the problem we are trying to solve?

To gain an improved understanding of how PRRSV **enters**, **replicates** and **survives** in and is **released** from infected cells

Challenge(s)

What are the scientific and technological challenges (knowledge gaps needing to be addressed)?

PRRSV infects macrophages which are an important contributor to the immune response so establishing how the virus interacts with macrophages is central to identifying the protective mechanisms and how the virus evades them.

Solution Routes

What approaches could/should be taken to address the research question?

Establish the basis of virulence/pathogenicity - including in high virulence strains – is it related to related to inflammatory response or viral replication
Viral and macrophage gene expression in different in vivo environments (macrophages from naïve and immune hosts)
Comparative response to highly pathogenic/virulent and mild/attenuated strains of the virus
Role of GP5 and Protein M peptides and binding.

Dependencies

What else needs to be done before we can solve this need?

The genome sequence of various PRRSV isolates

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Role of GP3 in infectivity
miR-181 and CD163 expression
Role of GP2a and GP4 in viral attachment