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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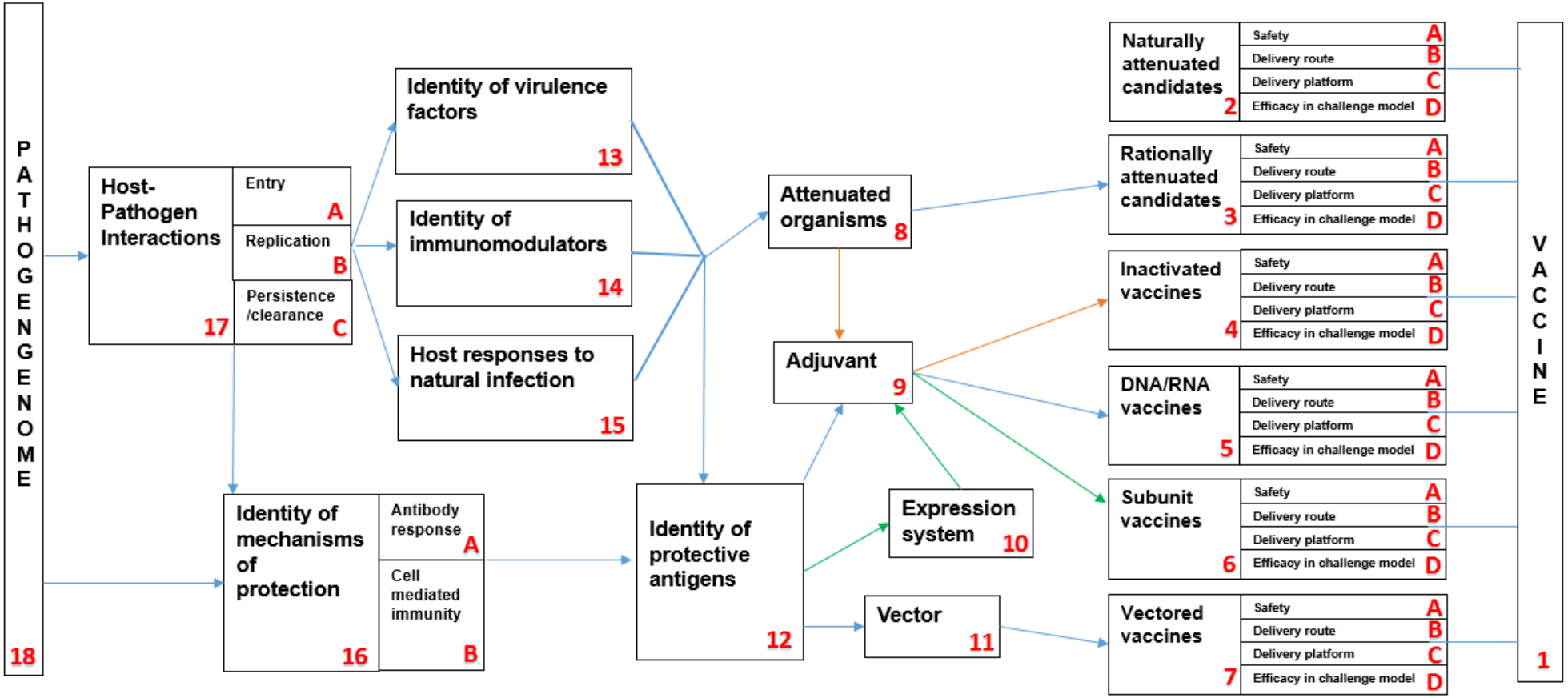
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Roadmap for development of a candidate vaccine for bTB

Version 1, 31/03/2018

Lead Summary 1

Title:	bTB 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 against bTB, reducing R_0 to <1 and allowing vaccinated to be differentiated from infected

Challenge(s)

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

Vaccines can sensitise animals to current diagnostic tests resulting in false positives.
The current BCG vaccine needs to be validated
Availability of a standardised BCG
The development of a better vaccine based on the rational attenuation of the organism or on purified immunogens delivered by various mechanisms

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**.
In particular establishing the level of protection given by BCG vaccination as a base line to compare other vaccines with
Establish if bovine genetics influences responses

Dependencies

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

Validation of BCG
Development of a novel attenuated vaccine that isn't excreted
Development of a subunit vaccine
Development of a DNA vaccine
Development of a cross protective vectored vaccine

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 2D

Title:	Validation of BCG efficacy

Research Question

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

BCG needs to be validated in relation to its efficacy in controlling bovine TB for a) its immediate deployment and b) to serve as a base-line against which other vaccines are compared.

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?

Establish the most effective vaccination regimen – dose, number of vaccinations, route of administration and optimal age for administration.
Vaccination, monitoring of immune responses and experimental challenge
Field trials

Dependencies

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

Agreed challenge models
Correlates of protection

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 3

Title:	Development of a novel attenuated vaccine allowing DIVA

Research Question

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

The development of a novel attenuated vaccine that gives better protection than BCG and allows differentiation of infected and vaccinated animals

Challenge(s)

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

Which strain of the organism to start with
Slow growing organisms in culture

Solution Routes

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

Establishing the immune responses to genetically modifies M Bovis and BCG
Challenge experiments involving animals vaccinated with candidate organisms.

Dependencies

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

The generation of GM organisms where the genes for selected virulence factors have been removed.
The genome sequence of M Bovis strains

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 5

Title:	Development of a DNA vaccine for bovine TB

Research Question

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

The development of an effective DNA vaccine for use on its own or in combination with other bovine TB vaccines in a prime-boost combination.

Dependencies

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

Identifying a combination of protective antigens the genes for which could form part of a DNA vaccine
Identifying suitable molecular adjuvants to stimulate strong cell-mediated immune responses

Challenge(s)

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

State of the Art

Existing knowledge including successes and failures

Solution Routes

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

Establishing the immune responses following immunisation with DNA coding for various protective antigens.
Challenge experiments involving animals vaccinated with DNA fragments identified from experiments looking at the immune responses.

Projects

What activities are planned or underway?

Lead Summary 6

Title:	Development of a bovine TB 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 for use on its own or in combination with other bovine TB vaccines in a prime-boost combination.

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?

Establishing the immune responses to the various subunits
Challenge experiments involving animals vaccinated with subunit candidate vaccines that resulted in interesting immune responses.
Establishing that there isn't interference between the various antigens

Dependencies

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

Identifying a combination of protective antigens for expression by a suitable expression vector
The availability of suitable adjuvants to stimulate strong cell-mediated immune 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 vectored bovine TB 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 novel vaccine. A replicating organism expressing the correct combination of Ags is more likely to generate the required type of immune response but as it would have a restricted combination of TB antigens it is unlikely to give false positive test results in the standard skin test

Challenge(s)

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

Generating a strong protective immune response
Preventing the development of immune responses to the vector

Solution Routes

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

Establishing the immune responses to the M bovis antigens following vaccination with the vectored vaccine.
Establishing the immune responses to the vector
Challenge experiments involving animals vaccinated with candidate organisms.

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 a suitable vector

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 8

Title:	Genetically modified M bovis

Research Question

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

Rational attenuation of M bovis by removing virulence genes so that it protects against infection but doesn't cause disease.

Challenge(s)

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

That the GM bacterium is stable and can be grown in culture

Solution Routes

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

Removal of one or more virulence genes and establishing viability and virulence and immunogenicity of the resulting organism

Dependencies

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

Identity of virulence factors
Identity of immunomodulatory factors in the bacterium
Identity of immunogens responsible for PPD skin sensitisation

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 vaccine candidates and DNA vaccine candidates

Research Question

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

Generation of an optimal immune response to the various sub-unit candidates and DNA 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?

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

Dependencies

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

Identity of protective mechanisms

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 Antigens

Research Question

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

Generation of a protective responses without the presence of possible virulence factors and or components responsible for skin sensitisation. Replicating organisms are likely to give the best immune response but attenuated M bovis may interfere with diagnostic tests

Challenge(s)

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

That the M bovis antigens are presented in a similar way to how they are presented by M bovis

Solution Routes

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

Generation of genetically modifies organisms (viruses or bacteria) expressing possible protective antigens of M bovis
Preparation of bacterial spores with the possible protective antigens of M.bovis adhered to the surface.

Dependencies

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

Identity of the protective antigens

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 12

Title:	Establishing the identity of protective antigens of M bovis

Research Question

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

The identity the M bovis components that the host needs to respond to to **prevent** and **contain** infection

Challenge(s)

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

Differentiating protective antigens from other antigens that the host is responding to which may be assisting the bacterium evade the hosts' responses at a particular stage of infection.

Solution Routes

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

To identify the antigens that are responsible for protective cellular responses.
The identity of the antigens that the host is generating Abs to and their role in protection (preventing and clearing infection).
Identifying possible protective antigens in the M bovis 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 cell-mediated immune responses and Abs.
The genome sequence of various virus isolates

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 13

Title:	Identification of the M bovis virulence factors 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?

Generation of a range of knock-out bacteria where putative virulence factors have been removed and their use in experimental infections

Dependencies

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

Improved understanding of M bovis - macrophage interaction – M bovis 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 and stealth mechanisms operating in M bovis infections

Research Question

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

Pathogens manipulate the immune responses of the host in an attempt to survive. Establishing how M bovis manipulates the host's immune response will allow these factors to be removed and thus allow the hosts immune system to react to the organism in a different way, possibly enhancing protection

Challenge(s)

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

Identifying deleterious immunomodulatory factors from ones that would **appear** to be beneficial. Mycobacterial appear to drive responses in a Th1 direction so it is essential to establish how this benefits the organism.

Solution Routes

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

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

Dependencies

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

Improved understanding of M bovis-macrophage interaction – M bovis 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 15

Title:	Identification of the M bovis immunogens responsible for skin sensitisation to PPD

Research Question

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

Infection with M. bovis or vaccination with BCG results in positive skin responses to PPD. Identification of factors responsible for the skin sensitisation would allow them to be removed and if not contributing to immunity can be removed from rationally attenuated vaccine candidates.

Challenge(s)

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

Skin sensitisation may be the result of several factors interacting

Solution Routes

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

Characterisation of PPD
Identify the factors responsible for causing skin sensitisation and their genes (fractionation and use in sensitised animals - identify the amino acid sequences – identify the genes).

Dependencies

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

A better understanding of host responses and host-pathogen interactions

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 16

Title:	To identify protective mechanisms in M bovis 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 **containing** 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?

Comparison of the innate immune responses of animals that are genetically “resistant” versus susceptible.
To identify the role of CMI and Ab in providing protection against infection – passive transfer experiments; identity of cell types responding in recall responses.
To establish the role of the various cell types and cytokine responses in preventing/clearing infection
To characterise the cytokine and cellular responses in granulomas at different stages of infection – how are infections walled of and become dormant
Identify disease stage biomarkers
Identify biomarkers of immunity

Dependencies

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

An improved understanding of host pathogen interaction at the level of the infected cells.
The genome sequence of various M bovis isolates, BCG and M TB

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?

Lead Summary 17

Title:	Host Pathogen interaction in M bovis 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 M bovis **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)?

M bovis infects macrophages which are an important contributor to the immune response so establishing how the bacterium 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?

M bovis and macrophage gene expression(transcriptome/RNA sequence data) in different in vivo environments (macrophages from naïve and immune hosts)
Compare response where macrophages are infected with different M bovis strains, BCG and M tuberculosis looking at gene responses of the macrophage and the bacterium.
Comparison of the macrophage-bacteria response following clearance (is infection ever cleared or just walled off?), in latency(this may involve comparative studies involving different breeds or species) and in active infections

Dependencies

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

The genome sequence of various M bovis isolates, including BCG

State of the Art

Existing knowledge including successes and failures

Projects

What activities are planned or underway?