Terms of Reference

A scour worm vaccine for sheep

(MDC applications only considered)

Summary

An effective vaccine against a parasite requires an antigen that elicits an immune response, against the parasite in question, targeted at the parasite's site of infestation. In the case of sanguiverous (blood sucking) parasites, it could be surmised that it is relatively easy to elicit a host response that produces circulating antibodies ingested by the parasite when it takes a blood meal.

Almost the entire Australian sheep flock is challenged by infestation with Small Brown Stomach Worm and Black Scour Worm (the "scour worms"), that are not primary blood suckers and hence, less susceptible to antibodies circulating in the blood stream. A literature survey commissioned by MLA (project B.AHE.0325) concluded that a vaccine against scour worms will need to elicit an immune response which is expressed at the site of infestation – the mucosa of the abomasum (in the case of *Teladorsagia circumcincta*) and the small intestine (*Trichostrongylus* spp.). It is unlikely that only antibodies (a humoral response) will suffice, and more likely that cellular immunity will be needed to have the desired effect.

The challenge is to find the right antigen, ensure that the response it elicits is expressed at the site(s) of infestation, and has an effect that leads to the death or inactivation of the parasite.

Program of Work

Meat & Livestock Australia (MLA) invests in research, development and adoption (RD&A) initiatives that contribute to programs of work to increase the productivity, profitability and sustainability of the grassfed beef and sheepmeat sectors. Proposals are sought for developing and executing collaborative and participative research to fit within this program of work.

Internal parasites have the costliest impact of all endemic conditions on profitable sheep production. Worm control continues to rely heavily on the use of chemicals, despite their cost and their diminishing efficacy in the face of worm resistance. Integration of alternative methods of internal parasite management, such as pasture spelling, rotational grazing and host alternation, requires planning time and infrastructure that are often in short supply. Vaccination is simple and relatively inexpensive, and will reduce reliance on chemicals, if it were available. Whereas a vaccine against Barber's Pole Worm (Barbervax® in Australia) has been successfully commercialised, a vaccine against scour worms would be a potential game changer for Australian sheep producers.

A literature survey commissioned by MLA (project B.AHE.0325) concluded that the development, formulation and delivery of a successful vaccine against scour worms will need:

a. knowledge of the exact nature of the protective responses to be induced by the vaccine to be effective,
b. selection of the most appropriate suite of "protective antigens" inducing effective immunity and,
c. knowledge of the ability of different vaccine formulations (+/- adjuvants) to induce protective immune responses against gastro-intestinal nematodes in sheep mucosae, so that the optimal combination of antigen, delivery agent and mode of delivery can be used.

Several technical advances are in place or require development to facilitate the approach to these three components:

i. fully annotated genomes for *Telodarsagia circumcincta* and *Trichostrongylus* spp. (*T colubrifomis* as the representative species) to enable identification of antigens and pathways in the life cycle of the parasites,
ii. gene knockout technology to identify genes essential for parasite development/survival, and
iii. improved tissue culture systems for worm and host tissues, to enable high throughput validation of worm antigens, their effects on parasite metabolism, development and survival *in vitro*, and analyses of host-worm interactions (and the genes/ pathways involved).

This program of work will most likely only succeed with a staged approach, with short, medium and longer-term goals. In the short term, there are several ongoing activities with the potential for success. Recent progress with recombinant sub-unit proteins as vaccines, and the availability of low-cost sequencing technologies for both transcriptomic and genomic analyses, could enable a rapid and relatively low-cost cross-species bioinformatic analysis of the transcriptomes of all parasitic stages to search for homologues of these vaccine antigens. *In vivo* verification of inhibited establishment following vaccination with the carbohydrate larval antigen (CarLA) would signify initial progress. Testing intranasal delivery could reveal an alternate route of administration.

In the medium to longer term, investment in technologies such as RNAi gene silencing and CRISPR/Cas9 gene editing could provide the means to identify genes with essential function. Combined with bioinformatics data (genomic, transcriptomic, protein structural modelling, epitope prediction), vaccine development can focus on essential genes that are expressed in parasitic lifecycle stages, in accessible sites (e.g. worm intestine, surface, excretory-secretory system), and are predicted to encode strong immunogenic epitopes. Surgical approaches, supplemented by assays for host and parasite products, bolstered by genomic, transcriptomic and proteomic technologies, are needed to define critical stages and pathways of the host-parasite interaction where vaccines can intervene. Finally, the vaccine dose needs to be titrated to achieve the optimal balance between the proportion of responders in the vaccinated flock, and the % protection in terms of reduced worm burden.

Deliverables

Completion of one or more stages of the program of work outlined above, satisfying the requirements for identified target(s) for the immune response, identified antigen(s) to elicit the desired immune response, and proof of the efficacy of the vaccine(s) to prevent the establishment of pathological worm burdens in sheep faced with natural infestation challenge on pasture.

Applicants will develop and describe their deliverables in terms applicable to the development of a commercial product, capable of being synthesized/produced in commercial quantities, and supported by data required by regulatory authorities.

Scope

MLA Donor Company applications will be only considered (https://www.mla.com.au/about-mla/what-we-do/mla-donor-company/).

The principal beneficiaries of this work will be Australian sheep producers, but the work can be international in scope, and the deliverable capable of being deployed globally if required.
Collaborative teams across institutions are encouraged to apply to take advantage of complementary skills including research, development, adoption and expertise in the use of products/technologies.

Participation of producers and formal producer networks is encouraged, especially in setting and

reviewing the direction of research, development and adoption of practical, on-farm practices.

Confidentiality and intellectual property

The successful applicant will be required to enter into a standard agreement with MLA.

Applicants must identify any background intellectual property (IP) they bring to the project.

All data and cited references must be acknowledged appropriately in the final publication and it is the sole responsibility of the applicant to ensure copyright laws are not breached.

Where further information is available which may assist the successful applicant in meeting the requirements of the project, MLA will provide such information to the successful applicant.

MLA will share and discuss this proposal with producers, technical experts, other research organisations and research and development corporations. Please acknowledge this freedom to operate.

Deadline for submissions

Preliminary proposals must be received by MLA before 11.59pm (NSW time) Friday, 2 October 2020. Late proposals will not be accepted.

Use the preliminary proposal template to submit proposals electronically to MLA at: projectcall@mla.com.au

Preliminary Proposals will be acknowledged and recorded on the MLA project information system.

Applicants will be advised in writing of the success or failure of their Preliminary Proposal in January 2021.

Further information

If you have questions regarding these terms of reference, contact:

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