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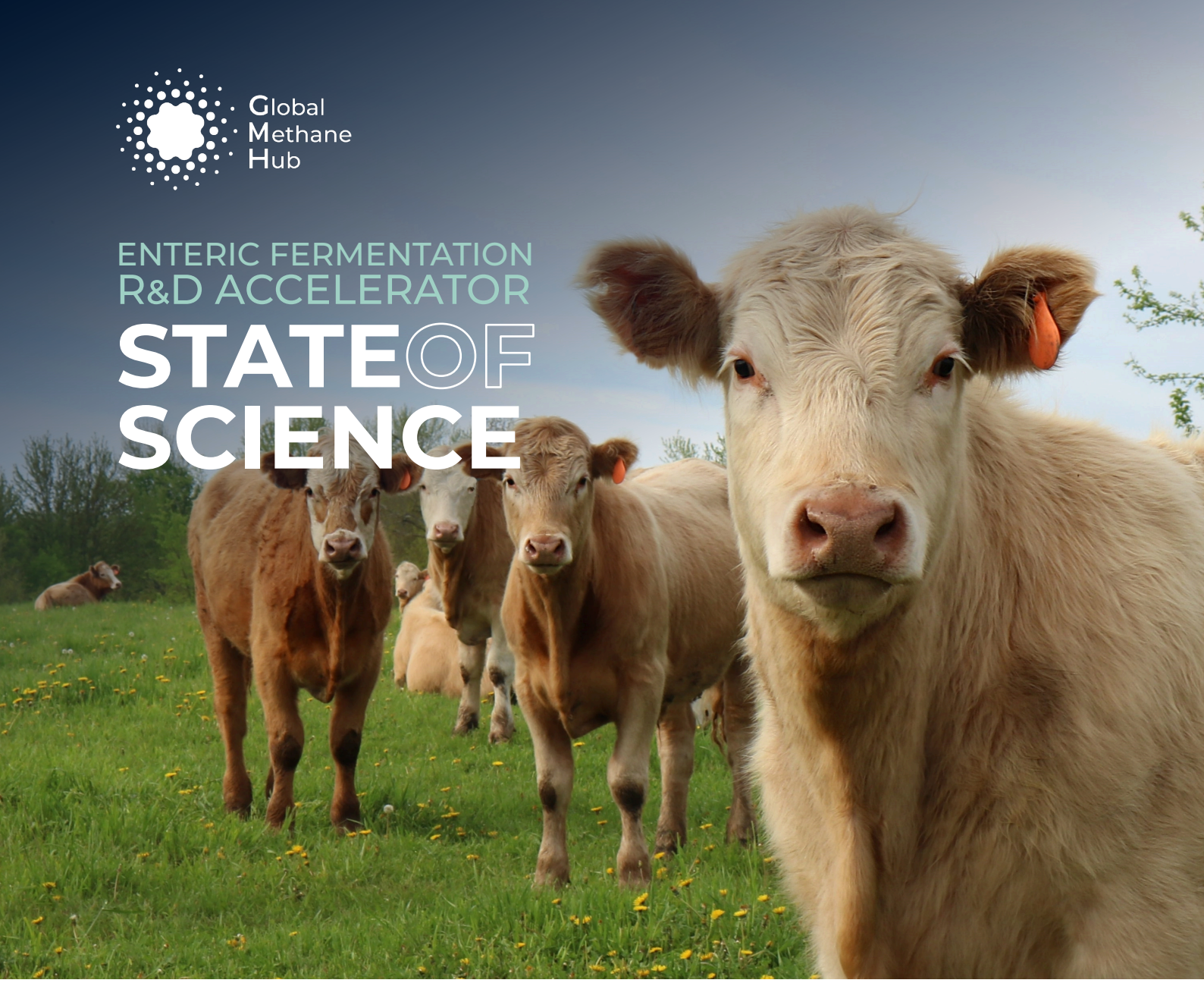

Methane Vaccines

Prepared By: Paul Wood, Updated July 1, 2024

While the concept of developing a vaccine to reduce methane production in ruminants has been discussed for over 2 decades the progress towards the development of a commercial product has been slow. There have also been only a few published papers in this field. To the best of our knowledge there are currently only two active research groups working on a methane vaccine, AgResearch (NZ) and Arkea Bio (Boston, USA).

Recently, The California Department of Food and Agriculture and the UC Davis College of Agricultural and Environmental Sciences organized the State of the Science Summit: Reducing Methane from Animal Agriculture in May 2024. This two- day conference included informational presentations and panel discussions with leading experts in methane mitigation and animal science. Dr Paul Wood, (Member of the Enteric Fermentation R&D Accelerator Science Oversight Committee of the Global Methane Hub) presented about anti-methane vaccine development and the link for the presentation can be found here: Developing Vaccinations to Mitigate Methane Emissions from Animal Agriculture in New Zealand (youtube.com)

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For development of a commercial vaccine the following steps are required.

1. Antigen identification, which organisms to target and do they express any major proteins that can be used as antigens. Methane is produced in the rumen by a group of archaea organisms called methanogens. These are a diverse group and only a few have been cultured in vitro. Therefore, a methane vaccine is likely to need to induce antibodies to at least the four major organisms to produce a sustained reduction in methane production. The level of cross-reactivity of antibodies to proteins within this group of organisms is not fully known.

2. Vaccine formulation, what adjuvant, how do you produce the antigens e.g., recombinant proteins, synthetic peptides or whole organisms. Traditional vaccines to bacteria are produced using whole organism or toxins produced by some bacteria. While sub-unit vaccines have worked very well with most viruses due to the dominance of key proteins, this has not been the case for bacteria or parasites. To enhance the immune response to vaccines a range of adjuvants have been used and most veterinary vaccine companies have their own propriety adjuvants for different species. The alternative to using adjuvants is to use a delivery vehicle, such as a viral vector or more recently mRNA. The approach of attenuating a pathogen to produce a live vaccine is unlikely to work due to the inability to grow most methanogens.

3. Challenge models, both in vitro and in vivo. There are in vitro systems for testing the effect of antibodies on the growth of selected methanogens that can be cultured, but these have not been correlated with in vivo models due to the variability in results. A reliable in vivo model to test a vaccine that demonstrate a significant impact on methane production will be required.

4. Assay systems, Antibody assays, Quality Control assays for the antigens. For commercial production of a vaccine a wide range of assay systems to quantify both the antigens and antibody responses to these antigens are required for manufacturing and safety and potency testing. This will require a set of monoclonal antibodies to key proteins included in the vaccine.

5. Vaccine stability. In general, commercial vaccines have a shelf-life at 4 degrees of several years, which has to be demonstrated with long-term stability trials. The minimum acceptable shelf-life for a commercial product would be one year. Currently mRNA vaccines need to be stored at minus 20 C, which one of the reasons that could restrict their use in veterinary species.

6. Vaccination schedule, number of doses, timing between doses, annual boost and age of animals. The ideal vaccine is one shot for life, but this is highly unlikely with a killed or sub-unit vaccine. The most commonly used vaccines in ruminants are the multivalent clostridial vaccines that require two doses for priming and an annual booster. Vaccination starts early in an animal's life to coincide with other production processes. There is a suggestion that vaccination of very young animals might produce a more long-lived shift in the microbiome of animals.

7. Safety and efficacy studies. Reactions at the site of vaccine injection are the most common side effect in ruminants and hence a safety profile of no greater reactions than those seen with clostridial vaccines would be required.

8. Registration process in major markets. As methane production is not a disease, in the USA the FDA will be the registration body. The boar taint vaccine developed by Zoetis was the first veterinary vaccine to be registered by the FDA rather than the USDA, as it was not considered a disease. In other major markets there should be no issues with registering a methane vaccine, as long as the claims made for this vaccine can be demonstrated.

Overall, the greatest technical challenge for an effective methane vaccine is to produce a long-lived antibody response that results in high concentrations of antibody in saliva. Cattle generate 1.5-2.5 rumen volumes (volume of a cows rumen is 80L) of saliva each day and thus vaccinated animals could continuously deliver anti-methanogen antibodies to the rumen. The immune system is not programmed to produce specific antibodies on a continuous basis unless there is an on-going antigen stimulus, therefore some form of antigen depot or in vivo antigen production will be required.

RELEVANT LITERATURE

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