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Novel methods for assessing the efficacy of vaccines against Johne's Disease

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Johne's Disease is caused by *Mycobacterium avium* subspecies *paratuberculosis* (*MAP*), a facultative intracellular bacterium that infects the intestine of ruminants resulting in granulomatous enteritis, wasting and eventual death (Chiodini et al., 1984; Harris and Barletta, 2001; Sweeney, 2011). The disease has a significant economic impact on producers in some parts of Australia, with Ovine Johne's disease accounting for losses of up to $13000 annually per infected property (Bush et al., 2006).

Vaccination has been at the forefront of Ovine Johne's disease control measures since the Australian Pesticides and Veterinary Medicines Authority approved Gudair™ (Zoetis, formerly Pfizer) for use in Australia in 2004 (Reddacliff et al., 2006). Gudair™ is able to reduce mortalities in heavily infected properties by up to 90% and delays the onset of faecal shedding (Reddacliff et al., 2006). However the vaccine is unable to provide complete protection. A proportion of vaccinated animals will still become infected and can shed bacteria in the faeces contributing to pasture contamination and hence transmission of *MAP*. In sheep, some infected animals can shed enough infectious doses to theoretically infect roughly 80 million sheep per day (Brotherston et al., 1961; Reddacliff et al., 2006; Whittington et al., 2000). Therefore there is a need for further research on vaccine development in order to obtain better control of the disease in Australia.

Historically, identification of successful vaccine candidates have been through trial and error methodologies which rely mainly on comparing the rates of clinical disease and infection in vaccinated and control individuals. Due to the slow progression of Johne's disease, this style of vaccine assessment can take years to get measurable results. Hence it is important that vaccine assessment methodologies be improved in order to reduce the time and increase the number of vaccines that can be examined within a given budget. Improvements can be made through coupling the study of immunological profiles produced by vaccination with final disease outcome. This dual approach will allow understanding of what constitutes a protective immune response, which will in turn permit better targeting of vaccines during their early development. Similar to other intracellular pathogens, a protective immune response to *MAP* is believe to be associated with host adaptive cellular immunity, however this has not be definitively proven.

My initial PhD research focuses on the development of a cellular assay to assess new vaccine formulations. This assay is adapted from a method described by Pascalis et al (2012). Briefly, monocytes from a vaccinated sheep are infected *in vitro* with *MAP*. These cells are then exposed to lymphocytes from the same animal. It is hypothesised that if vaccination of the animal has primed host lymphocytes to enable successful control of *MAP* infection, this will be reflected in the *in vitro* assay by destruction of *MAP* through interactions between the lymphocytes and monocytes. Currently I am assessing ways of detecting survival of *MAP* during the assay, and developing an in vitro infection model. My study is supported by an Australian Postgraduate Award and MLA top up scholarship and is linked to MLA project P.PSH.0576.

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