



Fasciola hepatica vaccine: We may not be there yet but we're on the right road



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ABSTRACT

Major advances have been made in identifying potential vaccine molecules for the control of fasciolosis in livestock but we have yet to reach the level of efficacy required for commercialisation. The pathogenesis of fasciolosis is associated with liver damage that is inflicted by migrating and feeding immature flukes as well as host inflammatory immune responses to parasite-secreted molecules and tissue damage alarm signals. Immune suppression/modulation by the parasites prevents the development of protective immune responses as evidenced by the lack of immunity observed in naturally and experimentally infected animals. In our opinion, future efforts need to focus on understanding how parasites invade and penetrate the tissues of their hosts and how they potentiate and control the ensuing immune responses, particularly in the first days of infection. Emerging 'omics' data employed in an unbiased approach are helping us understand liver fluke biology and, in parallel with new immunological data, to identify molecules that are essential to parasite development and accessible to vaccine-induced immune responses.

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1. Introduction

According to the United Nations, the world population will increase to 9 billion by 2050. The demand for animal-derived food, which has been growing at a rate of >7% over the last two decades, will correspondingly increase, both in developed and developing countries (FABRE Technology Platform working group). Therefore, going forward, to support this population growth, we need to secure a sustainable means of producing the quantity of food required,

and we need to do this in a safe and ethical manner to protect the consumer, the health and welfare of animals and our environment (Foresight, 2011).

This global population growth will open up attractive market prospects for countries with the capacity and technology to produce large quantities of high-quality animal products (particularly beef, dairy, pig and sheep). The value of farm-level animal production to the EU is over €130 billion; farmers represent >8% of the workforce, and farms employ >15 million people (FABRE Technology Platform working group, 2025). As farming intensifies, however, issues surrounding disease control, the prevention of disease transmission from animals to humans (zoonosis), the health and welfare of animals and the quality/safety of

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the food we consume will come to the forefront (FABRE Technology Platform working group; Meat & Livestock Australia: <http://www.mla.com.au>).

Ireland is a good example of a small European country whose economy depends heavily on agriculture and at the same time has the ability to take advantage of these future trends. Irish agriculture is primarily a grass-based industry; of the total land area of 6.9 million hectares, 4.2 million (64%) is devoted to agriculture, 90% of which is pasture. There are about 6.5 million cattle in Ireland and the Irish sheep flock exceeds 4.8 million head, with a breeding flock of 2.51 million head. During 2011, 548,000 tonnes of beef and 37,000 tonnes of sheep meat were produced, most of which was exported. Each year, 17,000 dairy farms produce 5.4 billion litres of milk (Teagasc). These figures provide a snapshot of how important the livestock industry, altogether valued at €5–6 billion per annum, can be to a small economy such as Ireland's with a population of under 5 million (Bloemhoff et al., 2014).

2. Parasitic diseases impact hugely on the animal production industry

Helminth parasites cause >55% of all farm animal diseases in Europe and effective control strategies would have a major impact on the sustainability of the livestock industry (Nieuwhof and Bishop, 2005; Murphy et al., 2006; Morgan et al., 2013). In Europe, parasitic diseases of farm animals are caused principally by infections with the liver fluke *Fasciola hepatica*, the lungworm *Dictyocaulus viviparus*, and the gastrointestinal nematode parasites of sheep (*Haemonchus contortus*, *Teladorsagia circumcincta*) and cattle (*Ostertagia ostertagi*, *Cooperia oncophora*). These parasites impact on livestock productivity by affecting growth rates, fertility and the quality of wool and milk production. In particular, during seasons of major fluke outbreaks, infection can result in many animal fatalities (Piedrafita et al., 2010). In general, about 17% of animal production is estimated to be lost through infection of livestock with pathogens including these parasites (FABRE Technology Platform working group).

The losses to the livestock industry as a result of parasitic helminths are compounded by the significant effort and cost of trying to control these infections with regular chemical treatments. Within Europe, the annual spend on anthelmintic drugs for parasitic helminths of ruminants has been estimated to be €400 million (Selzer, 2009; Morgan et al., 2013). These costs contribute to the overall economic losses related to disease, which for *F. hepatica*, in particular, are estimated to be US \$3 billion globally (Spithill et al., 1999a; Mas-Coma et al., 2005; Piedrafita et al., 2010). However, anthelmintic resistance, especially in gastrointestinal nematode parasites (Kotze et al., 2014), has spread to the point that it is now a global concern and is already impacting significantly on livestock productivity in many regions. Resistance is also becoming a serious issue in liver fluke (Fairweather, 2011; Dalton et al., 2013). The use of chemical products to control parasitic infections is, therefore, not sustainable in the long term because of the likelihood of continual emergence of drug-resistant parasite populations. Additionally, there are growing consumer

concerns about chemical residues in food, and also the detrimental impact they have on the environment (Dalton and Mulcahy, 2001; Cooper et al., 2012). In particular, an assessment report adopted by the Committee for Medicinal Products for Veterinary Use (European Commission) has recently established maximum residue limits for triclabendazole (TCBZ) in bovine and ovine milk, in addition to those already set for ruminant muscle, fat, liver and kidney (EMA, 2012). Recent flukicide licensing restrictions for lactating dairy cows only allow the use of albendazole (ABZ) and oxclozanide (OCZ) for fluke control (HRPA, 2013). Unlike TCBZ which is active against both immature and adult parasites, ABZ and OCZ have restrictive activity against the adult parasites and use of these anthelmintics often requires repeated treatments, which are not always carried out in the field (Fairweather and Boray, 1999; Power et al., 2013).

Vaccines, on the other hand, are considered safe and are acceptable to both users and consumers. New vaccine technologies and adjuvant development are further improving food safety by ensuring that these leave no residues in food (Parker et al., 2009; Adams et al., 2009). As no chemical residues are passed onto pasture, vaccines are also considered environmentally friendly. However, despite the huge successes we have made in vaccine development against viruses and bacteria over the past 200 years (and in recombinant vaccines in the last 30 years), with the exception of the live attenuated Huskvac vaccine for lungworm, there are no commercially viable vaccines for animal (or human) helminth parasitic pathogens. More recently, a new vaccine for *H. contortus*, Barbevax, consisting of native gut-derived antigen complex has been launched in Australia (www.barbevax.com.au).

3. Liver fluke disease: a food-borne zoonotic disease

Liver fluke disease, or fasciolosis, in sheep and cattle results from infection with the trematode, *F. hepatica* (Andrews, 1999). Due to the emergence of parasites resistant to the frontline drug triclabendazole (TCBZ) and also to climate changes favourable to the survival of the intermediate host (*Galba truncatula*) and the infective stage (metacercariae) of the parasite (Piedrafita et al., 2010), consistently high prevalence levels of liver fluke have been recorded across Europe (recently reviewed by Charlier et al., 2014). Within the UK, the prevalence of fasciolosis has shown a marked increase, specifically in dairy herds from 48 to 72% from 2003 to 2006 (McCann et al., 2010) and, more markedly, the distribution of liver fluke has spread to include areas of Scotland and East Anglia (Pritchard et al., 2005; Kenyon et al., 2009). The increased prevalence of *F. hepatica* further adds to the economic impact of this parasite and indicates that the potential losses are greatly under-represented.

F. hepatica is also an important pathogen of humans in certain regions of the world where farm management practices allow infected animals to roam amongst vegetation consumed by humans. Global human infections are estimated to be between 2 and 17 million with 180 million people at risk; prevalence is particularly high in the Andean Altiplano (Bolivia, Peru and Ecuador) with lower

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