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Review

Recombinant vaccines against bluetongue virus☆

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A B S T R A C T

Bluetongue (BT) is a hemorrhagic disease of ruminants caused by bluetongue virus (BTV), the prototype member of the genus Orbivirus within the family Reoviridae and is transmitted via biting midges of the genus Culicoides. BTV can be found on all continents except Antarctica, and up to 26 immunologically distinct BTV serotypes have been identified. Live attenuated and inactivated BTV vaccines have been used over the years with different degrees of success. The multiple outbreaks of BTV in Mediterranean Europe in the last two decades and the incursion of BTV-8 in Northern Europe in 2008 has re-stimulated the interest to develop improved vaccination strategies against BTV. In particular, safer, cross-reactive, more efficacious vaccines with differential diagnostic capability have been pursued by multiple BTV research groups and vaccine manufacturers. A wide variety of recombinant BTV vaccine prototypes have been investigated, ranging from baculovirus-expressed sub-unit vaccines to the use of live viral vectors. This article gives a brief overview of all these modern approaches to develop vaccines against BTV including some recent unpublished data.

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1. Introduction

Bluetongue virus (BTV) was first detected in 1900, when Merino sheep were imported into South Africa and became infected (Spreull, 1905) showing clinical signs of hemorrhagic disease. This virus belongs to the *Orbivirus* genus, within the family *Reoviridae* and has a double stranded RNA genome that encodes four non-structural (NS1–NS4) and seven structural proteins (VP1–VP7) (Mertens et al., 1984; Mertens, 1986). The genome segments are packaged within an icosahedral capsid, ~80 nm in diameter, composed of three concentric protein layers. The innermost 'subcore' shell is constructed from 12 decamers of VP3, surrounding the virus genome and viral transcriptase complexes, and provides a 'scaffold' for addition of 780 copies of VP7 (organized as 260 trimers) to form the core-surface layer. The addition of 60 trimers of VP2 and 120

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trimers of VP5 which form the outer capsid layer, complete the virion structure (Roy, 1989).

The efficient transmission of the virus by *Culicoides* midges in areas with suitable vector species results in a fast spread of the disease. The disease has been devastating for European cattle and sheep especially since 1998 after repeated BTV outbreaks caused by 6 of the 26 different serotypes (Darpel et al., 2007; Maan et al., 2012). This has resulted in a big impact on trade and agriculture, making very important the development of new safe and effective vaccines against the virus.

Modified live vaccines have long been used to control BT in sheep in southern Africa, and more recently in Corsica, the Balearic Islands and Italy (Savini et al., 2008). Although live attenuated vaccines appear to be effective for protection of individual susceptible animals against clinical signs of bluetongue, they are teratogenic and cause other adverse effects (IZSAM, 2001; Veronesi et al., 2010). Moreover, the vaccine virus can be detected in blood after vaccination and reaches titers that are compatible with transmission to other mammalian hosts via *Culicoides* midges (Elia et al., 2008). When vaccine virus is transmitted to unvaccinated animals (Ferrari et al., 2005; Savini et al., 2008) there is a further risk of genome segment re-assortment between vaccine and field strains, leading to the emergence of new strains with unpredictable biological characteristics (Batten et al., 2008).

Whole inactivated virus vaccines represent a safer alternative to live attenuated vaccines and are commercially available but some concerns exist over the reliability of inactivation for each vaccine batch (Gethmann et al., 2009). Inactivated BTV vaccines have prevented the re-emergence of the disease in northern Europe in the years that followed the 2008 outbreak, however the cost of production of inactivated vaccines is high and various boosters are necessary to achieve solid immunity.

Serological screening techniques are essential for the surveillance of the disease in non-endemic countries when a vaccination campaign is followed and to demonstrate freedom of the disease once the outbreak has ended. There is currently not a reliable serological test to "distinguish infected from vaccinated animals" (DIVA assays) when either inactivated or attenuated BTV vaccines are used. For these reasons the development of recombinant BTV vaccines, which are inherently safer, and are based on selected BTV antigens and are therefore compatible with a DIVA approach, has been the subject of research over more than two decades. This review describes novel advances in the development of recombinant vaccines against BTV and the different studies testing their protective efficacy.

2. New-generation vaccines against BTV

Different strategies have been followed over the last 3 decades to develop novel recombinant vaccines for BTV, ranging from baculovirus expressed sub-unit vaccines to live virus vector vaccines (Table 1).

Immunological studies to date have given many clues about what BTV proteins are more important to induce protective host immune responses against the virus. The cellular receptor binding protein VP2 induces serotype specific neutralizing antibodies (Huismans and Erasmus, 1981) and protective immunity (Huismans et al., 1987). Epitope mapping studies revealed that the major virus neutralizing epitopes are located in the protein VP2 (Roy, 1992). This protein is the most variable protein among BTV serotypes and is the determinant of the serotype (Mertens et al., 1989). Antibodies raised against VP2 can sometimes neutralize, although less efficiently, other very closely relates serotypes (Roy, 1992). However 26 serotypes of BTV have been reported (Maan et al., 2012) and low levels of cross-protection are described, complicating vaccination strategies. VP5 protein is the second most variable of the BTV proteins and seems to exert some influence in the conformation of VP2 (Cowley and Gorman, 1989; Mertens et al., 1989). It has been demonstrated that both virus neutralizing antibody responses (Jeggo et al., 1984b) and cytotoxic T-lymphocytes (CTL) have a main role in protective immunity against BTV (Jeggo and Wardley, 1982; Jeggo et al., 1984a). BTV-specific CTL have been studied in sheep, describing VP2 and NS1 as major CTL targets (Andrew et al., 1995). NS1 was recognized by CTL from all Merino sheep immunized with recombinant vaccinia viruses, while VP2, VP3, VP5 and VP7 were recognized by CTL from only some sheep (Janardhana et al., 1999). In mice, statistical analysis of the CTL responses indicated that non-structural protein peptides were the predominant source of homotypic and heterotypic CTL recognition (Jones et al., 1996). In mice, T-cell epitopes (CD4 and CD8) were identified in the major BTV group-reactive antigen VP7 and these epitopes were also recognized by cells from BTV infected sheep (Rojas et al., 2011).

In general, vaccine approaches developed against viral diseases are preferably tested in a natural host. However, constraints imposed by the high cost of performing experiments in bio-containment facilities for large animals have led to the establishment of a small animal model for BTV (Calvo-Pinilla et al., 2009a). This murine model based on adult IFNAR (−/−) mice facilitates the study of the BTV immune responses and the testing of new vaccines against bluetongue. IFNAR (−/−) mice are lack the β-subunit of the interferon α/β receptor and this model has been used successfully in various studies with orbiviruses (Calvo-Pinilla et al., 2010; Castillo-Olivares et al., 2011; Eschbaumer et al., 2012).

2.1. Subunit vaccines

Protein-based vaccines against BTV have been developed using single proteins or by combining various proteins in the same vaccine preparation. Huismans et al. (1987) isolated VP2 from purified BTV by chemical means using divalent salts. Vaccination of sheep with this protein induced virus neutralizing antibodies and protection against virulent homologous challenge (Huismans et al., 1987). Despite its efficacy, this strategy could not be developed further due to the large amounts of virus required to produce enough purified protein for use in a sub-unit vaccine formulation.

Table 1
Recombinant viral vector vaccines against BTV tested in IFNAR (−/−) mice.

Delivery viral vector	Proteins expressed	Protection homologous challenge	Protection heterologous challenge
Bovine herpes virus	VP2 BTV-8	Partial	Not analyzed
Equine herpes virus	VP2 BTV-8	No	Not analyzed
Equine herpes virus	VP2, VP5 BTV-8	Partial	Not analyzed
MVA virus	VP2, VP5 BTV-4	Partial	Not analyzed
MVA virus	VP2, VP5, VP7 BTV-4	Complete	No
MVA virus	VP2, VP5, VP7 BTV-4	Complete	Complete
MVA virus	VP7, NS1 BTV-4	Partial	Partial
MVA virus	VP2, VP5, VP7 BTV-8	Complete	Not analyzed
MVA virus	VP2 BTV-8	Complete	Not analyzed

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