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Review

Utilization of herpesviridae as recombinant viral vectors in vaccine development against animal pathogens

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ABSTARCT

Throughout the past few decades, numerous viral species have been generated as vaccine vectors. Every viral vector has its own distinct characteristics. For example, the family herpesviridae encompasses several viruses that have medical and veterinary importance. Attenuated herpesviruses are developed as vectors to convey heterologous immunogens targeting several serious and crucial pathogens. Some of these vectors have already been licensed for use in the veterinary field. One of their prominent features is their capability to accommodate large amount of foreign DNA, and to stimulate both cell-mediated and humoral immune responses. A better understanding of vector-host interaction builds up a robust foundation for the future development of herpesviruses-based vectors. At the time, many molecular tools are applied to enable the generation of herpesvirus-based recombinant vaccine vectors such as BAC technology, homologous and two-step en passant mutagenesis, codon optimization, and the CRISPR/Cas9 system. This review article highlights the most important techniques applied in constructing recombinant herpesviruses vectors, advantages and disadvantages of each recombinant herpesvirus vector, and the most recent research regarding their use to control major animal diseases.

1. Introduction

In the last decades, the generation of recombinant vaccines has become a revolutionary research hot spot. It is one of the most exciting implications of the field of molecular virology. Live recombinant viral vaccine vectors have played a crucial factor in developing new and innovative vaccines. Some viruses such as poxviruses, adenoviruses, parvoviruses, flaviviruses, alphaviruses, newcastle disease virus (NDV) and herpesviruses have been used as viral vector vaccine. They are considered as potential beneficial tools for gene therapy and vaccines development. These viral vectors express heterologous genes against several diseases. Generally, the advantages of using viral vectors are not only limited to the delivery of foreign genes to target cells more specifically with high-efficiency gene transduction but also elicitation of robust immune responses and increasing cellular immunity (Ewer et al., 2016; Schultz and Chamberlain, 2008).

There is no doubt that the area of vaccinology is still ongoing. Understanding vector/host interactions needs more focus and investigation to solve many obstacles before viral vaccines will face widespread use. Pre-existing immunity versus the vector and the possibility to integrate into the host genome are the most crucial critical points (Ertl, 2016; Sakurai et al., 2008).

Many herpesvirus`s genomes have a thymidine kinase gene (*TK*) which is not necessary for virus growth in actively dividing cells (Field and Wildy, 1978), yet, it facilitates their growth in the non-dividing cells (Field and Wildy, 1978). Plenty of research has proved that the virus growth and replication are not affected in TK-defective mutants of herpes simplex virus (HSV) (Field and Wildy, 1978), equine herpesvirus-1 (Slater et al., 1993), pseudorabies virus (PRV) (Kit et al., 1985a; Tenser et al., 1983) and bovine herpesvirus-1 (Kit et al., 1985b). However, these viruses are remarkably attenuated for their natural hosts or mice, and less readily reactivate from nerve cells (Efstathiou et al., 1989) therefore, their applications in vaccine development have been exploited.

This review will summarize the most important techniques used in generating recombinant herpesvirus vectors. In addition, the review will represent both advantages and disadvantages of each animal recombinant herpesvirus vector and discuss the future aspects of their use to control veterinary epidemics.

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2. Background information: structure of herpesviruses, genomic organization and utilized techniques in generating viral recombinants

2.1. Structure and genomic organization

Herpesviruses are virions comprising of four main structures; a core, capsid, tegument, and envelope. The genomic core is made up of a single, linear double-stranded DNA molecule(dsDNA) which is surrounded by capsid proteins having a 125 nm approximate external diameter in human herpesvirus 1 (Maclachlan and Dubovi, 2010; Pellett and Roizman, 2013). The capsid principally consists of 162 capsomers of 150 hexons and 12 pentons, a fibrous core with spool shape a torus shape wrapping the DNA genome (Maclachlan and Dubovi, 2010; Pellett and Roizman, 2013). The globular tegument layer is encompassed by an envelope carrying many glycoprotein spikes. The virions diameter varies between 120 and 250 nm due to the diverse size of the envelope (Maclachlan and Dubovi, 2010; Pellett and Roizman, 2013).

The genomes of the herpesviruses vary clearly in their size, structure, and organization reflecting the sophisticated taxonomic classification of this family. Their genomes are divided into unique small (US) and unique large (UL) by repeated sequences that generally take place at both ends (and in some viruses as well internally) (Borchers et al., 1994; Pellett and Roizman, 2013). Upon the orientated inversion of the repeated sequences, the UL and US components invert identical to one another during replication, generating 2 or 4 different genome isomers that exist in equimolar proportions (Pellett and Roizman, 2013; Roizman et al., 1981).

There are three fundamental types of the herpesviruses genes: immediate-early (IE) and early genes (E) encoding proteins having regulatory functions and pivotal for the virus to replicate, late (L) genes encoding structural proteins. Finally, it is important to note that there are “non-essential genes” within all three transcriptional classes that are not necessary for replication in cultured cells and have not been identified in all of the herpesviruses (Gruffat et al., 2016; Pellett and Roizman, 2013; Roizman et al., 1981). Herpesviruses virions comprise more than 30 structural proteins, of which six are existing in the nucleocapsid and two are DNA-associated (Maclachlan and Dubovi, 2010). The glycoproteins are projecting as spikes from herpesvirus envelope. Some immunomodulatory and growth-regulating proteins are not essential for virus replication in tissue culture and are cellular genes homologs encoding regulatory proteins associated with regulating the growth and modulating the immune response (Davis-Poynter et al., 1996; Nishiyama, 1996; Pellet, 2007; Pellett and Roizman, 2013). Herpesvirus genomes are mainly kept latent in host cells in the form of a circular episome. On the other hand but not as much often, the viral genomes may get integrated into the host chromosome (Morissette and Flamand, 2010).

2.2. Techniques used for generating recombinant herpesviruses

2.2.1. Bacterial artificial chromosome (BAC)

2.2.1.1. BAC and herpesviridae. BACs are artificial DNA constructs centered on a functional F-plasmid utilized for cloning large sizeable DNA in *Escherichia coli* (Shizuya et al., 1992; Warden et al., 2010). F-plasmids have greatly involved in constructing BACs as they enable even and equal distribution of plasmids and their inserts (ligated viral genome) in dividing bacteria. Owing to large sized herpesvirus genomes, their ligation in BAC plasmid is not an easy step. Shuttling BAC plasmid cassette into herpesvirus genome occurs through the ordinary homologous recombination in infected cells. Circularization of the linear dsDNA herpesvirus genome then occurs throughout their replication (Wagner et al., 2002). Afterwards, isolation of the BAC mutant circular replication intermediates is followed by its shuttling into the competent *E. coli* via DNA transformation. Propagation of herpesvirus BAC as well as the mutated one could then be accomplished in *E. coli*. BAC-viral DNA clone is subsequently transfected into permissive cells which results in virus reconstitution and infectious virus generation (She, 2003). The viral progeny are after that generated via transfecting the kept viral genome in *E.coli* via BAC system through their reconstitution in eukaryotic cells generating recombinant viral genomes with the inserted foreign gene of interest in a fast, easy and feasible way.

2.2.1.2. BAC technology application in generating herpesvirus-based vaccine vectors. Herpesviruses possess one of the largest DNA genomes within the mammalian viruses (McGeoch et al., 2006). Their large size leads to prodigious difficulties in their experimental manipulation (Zhou and Roizman, 2005). BAC technology has facilitated manipulation of large DNA genome and consequently several herpesviruses BACs have been constructed, for example, murine cytomegalovirus (MCMV), equine herpesvirus (EHV), PRV, HSV, and BHV (Mahony et al., 2002; Messerle et al., 1997; Rudolph et al., 2002; Saeki et al., 1998; Smith and Enquist, 1999). One of the most important applications of BAC technology is generating recombinant vector vaccines and the high advancement in related molecular biology. The convenience of cloned herpesvirus BACs was able to permit alteration of viral genomes by inserting or deleting sequences that make the BAC system a potent and efficient tool to deliver numerous genes from various infectious agents in the recombinant vaccine fields (Hall et al., 2012; Tai et al., 2016; Tan et al., 2017; Warden et al., 2011). The BACs technologies open the way to several applications such as expressing therapeutic genes in place of the non-essential genes making these viruses effective as vehicles in both vaccine development and gene therapy.

2.2.2. En passant mutagenesis

One of the established techniques to handle DNA viruses is the two-step en passant mutagenesis, which enables easy insertion, deletion, and mutation to the DNA virus BACs which are then transfected into eukaryotic cells generating the recombinant DNA viruses (Tischer et al., 2006). This technology has been used during the construction of recombinant EHV pRacH vaccine vector through two steps. During the first recombination step, inserting the amplified gene of interest into pRacH BAC under control of the human cytomegalovirus immediate-early (HCMV-IE) gene promoter is carried out leading to intermediates clones with kanamycin resistance. The obtained clones show the anticipated changes in the parental-type DNA restriction arrangement. Removal of the kanamycin gene is then achieved in the 2nd recombination step resulting in final recombinant equine herpesvirus type 1 (EHV-1) expressing the foreign gene (Tischer et al., 2006) as shown in Fig. 1

2.2.3. Homologous recombination

Homologous recombination (HR) techniques have been extensively used in generating recombinant DNA, viral vectors, and genetically modified organisms by inserting foreign DNA fragments into the viruses. It occurs between the transfer plasmid and viral vector genome to transfer the foreign gene(s) of interest of the infectious agent (Fig. 2). It has also been employed as a tool in gene therapy.

HR in bacteria has been introduced to produce a self-excisable canine herpesvirus (CHV) BAC plasmid during the bacterial replication following transfecting BACs into cell culture (Strive et al., 2007). It has also been employed in various recombinant herpesviruses vectors during their generation such as the recombinant Marek (Zhang et al., 2014), pseudorabies (Li et al., 2008), bovine herpesvirus 1 genomes (Mahony et al., 2003) and turkey herpesviruses (Liu et al., 2019).

The steps of HR including insertion of marker genes and subsequent recombination experiments to remove the marker gene to get the recombinant virus, notwithstanding the selection of these recombinant viruses frequently require a laborious process, plaque purification,

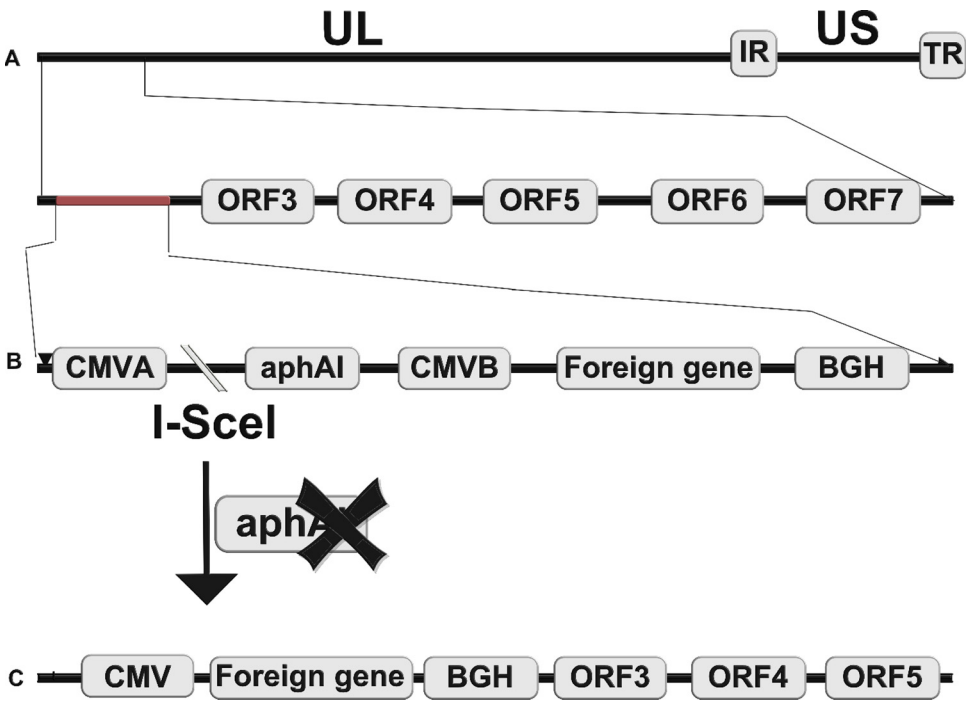

Fig. 1. Application of Two-step red-mediated recombination in constructing equine herpesvirus viral vector against many diseases including insertion of the recombination cassette containing the gene of interest, promoter and selection marker, kanamycin in the deleted ORF1/2 of the pRacH BAC representing the first step in recombination which is followed by removal of the selection marker in the second step.

getting rid of parent virus and assuring propagation of only a single virus population. Steps of HR are illustrated in Fig. 2.

2.2.4. Codon optimizations in vectrology

Synthetic codon optimization of the inserted sequence of interest is recently utilized in generating recombinant viral vectors to enhance its protein expression in the living organism. Transgenes with codon optimization for mammalian expression are the best choice to enhance gene functionality throughout elevating its translational efficiency by transforming DNA nucleotides sequence of one species into DNA nucleotides sequence of another species (Inouye et al., 2015; Mauro and Chappell, 2018). The amino acid will remain finally the same, but with a codon of high frequency substituting the low-frequency codon of the amino acid (Błażej et al., 2017). The replacement of wild-type DNA

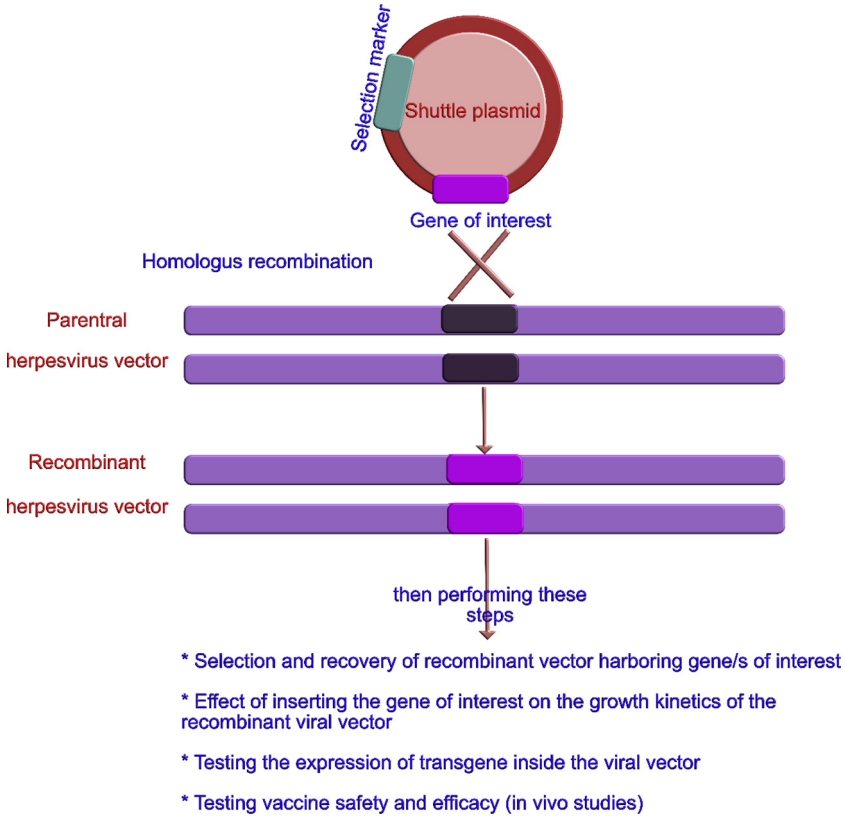

Fig. 2. Homologous recombination in vectrology; steps and downstreams for vaccine development.

sequences leads to more highly expressed species sequences. These high expressed sequences enhance the immunogenicity according to the desired species frequency distribution as changes of some triplets is found in each sequence of nucleotides of given species. While synthetizing an optimized codon gene, the concern of the codon usage is very crucial as each organism has its preferred choice of DNA nucleotide usage to encode any particular amino acid. Herpesviruses have unique codon optimization which effects gene regulation and presentation. Better immunogenicity to a protein may be achieved by altering the codons to match the codon usage of similar herpesvirus genes, rather than optimizing codon usage in the conventional sense. Actually, the viral properties following codon optimization had been explored in a limited number of studies (Coleman et al., 2008). Codon optimization of Marek's disease virus (MDV) does not affect their viral replication either in vitro or in vivo (Eschke et al., 2018). The increase in protein production following the optimization might produce more virulent or pathogenic virus than the wild type which still needs more and deep investigation (Eschke et al., 2018). Codon optimization has shown a great relevance in DNA vaccination for HIV (Giri et al., 2004; Ramakrishna et al., 2004). It has also been depicted that the genes that utilize rare codons are less well expressed than those use frequent codons. The relative frequency of using each codon can vary substantially between species, although certain codons are seldom in use across species. Although the resulting gene expression levels may affect the vaccine efficacy, they are sometimes not being correlated with the immunogenicity or vaccine efficacy.

2.2.5. CRISPR/Cas9 system and herpesvirus-based recombinant vaccines

The clustered regularly interspaced palindromic repeats (CRISPR)/Cas9 system has been recently introduced as a successful, versatile and specific tool in many gene editing settings. Manipulating many large DNA virus genomes involving herpesviruses is considered one of these vital settings (Chen et al., 2018; Tang et al., 2018b). CRISPR/Cas9 has enhanced the HR efficiencies between the PRV genome and a linearized transfer vector through double incisions and acted as a site-specific gene knock-in instrument (Guo et al., 2016). An effective and rapid CRISPR/Cas9-based genome editing has recently been developed for constructing recombinant herpesvirus of turkey (HVT) delivering the VP2 protein of infectious bursal disease (IBDV) by which The VP2 expression cassette is placed into the HVT genome through an NHEJ (nonhomologous end-joining)-dependent repair pathway and the green fluorescence protein (GFP) expression cassette is primarily introduced to the insert for convenient visualization and afterward eliminated through the Cre-LoxP system (Tang et al., 2018a, 2019). Via this system, incorporating other antigens inside the HVT genome leads to immediate design of recombinant vaccines. Another recombinant HVT harboring hemagglutinin (HA) gene from H9N2 (rHVT-H9) has also been recently generated through the CRISPR/Cas9 system which effectively protected chicken against H9N2 (Liu et al., 2019).

General merits of herpesvirus vaccine vectors

Several vaccines have been introduced as inactivated vaccines, live attenuated vaccines, DNA vaccines, peptide vaccines, vector vaccines (Kamel et al., 2019). The most common inactivated and live attenuated vaccines have many drawbacks for use. The safety issue of the live attenuated vaccines is its reversion to virulence that may happen. The incomplete humoral short course immunity, some viruses need high biosecurity levels during manufacturing, need for cold chain containment are representing the main demerits with respect of inactivated vaccines (Kamel et al., 2019). Unfortunately, both inactivated and live attenuated vaccines cannot differentiate infected from vaccinated animals which are compulsory in controlling pathogens. Advanced progress in the vaccinology era to substitute these vaccines with the molecular biology-based vaccines or vector vaccines are still ongoing to overcome their demerits. Herpesvirus-based vectors are considered one of these vaccines that have several merits for use in recombinant vaccine production. The herpesviruses have a higher safety concern due to their limited host range and the well-known attenuation. Several pathogens represent severe socioeconomic consequences affecting animal and poultry industry and may have a zoonotic importance such as foot and mouth disease, avian influenza virus, bovine viral diarrhea, blue tongue, and many others. Delivering immunogenic viral structural proteins can be easily accomplished using herpesvirus-based viral vectors to provoke a strong cell-mediated and humoral immune response in the vaccinated animals via expressing in the vector-infected cells. Herpesviruses harbor several insertion sites within their large genomic make-up organization where they can tolerate several large sizeable foreign genes of interest to be inserted and perfectly expressed within the host without any noticeable deleterious impact on their replication provoking a strong cell-mediated and humoral immune response in the vaccinated animals. Another merit is their differentiating infected from vaccinated (DIVA) capability which is very pivotal in pathogens control and eradication. Their easy mass production adds another economic merit for use in veterinary medicines. Herpesviruses are also safe to vaccinate, stably express the foreign genes successfully and can withstand the environmental conditions so no cold chain conditions are required

3. Animal herpesviruses in both research and commercial studies as recombinant viral vectors

3.1. Canine herpesvirus

Canine herpesvirus (CHV) belongs to Alphaherpesvirinae subfamily in the Herpesviridae family (Papageorgiou et al., 2016). Although it is not a life-threatening disease of adult dogs induces only mild or undetectable clinical signs, it causes severe fatal generalized necrotizing and hemorrhagic lesions of less than 14 days old puppies (Blakeslee et al., 1885). Their transmission mode through placenta is also established resulting in fetal death (Hashimoto et al., 1982). Although several surveys have demonstrated a high CHV prevalence in the household and colony-bred dogs, its fertility problems are usually restricted to the inbreeding dogs (Reading and Field, 1999; Ronsse et al., 2002). Due to its low inherent virulence, gene deletions, and the availability of virus mutants, CHV is an ideal candidate to be used as an attenuated recombinant viral vector vaccine to protect dogs from CHV and a broad range of pathogens (Haanes and Tomlinson, 1998). In addition, it can also be used in gene therapy of domestic dogs because of its safety in other species as its host range is restricted only to dogs with low pathogenicity in adult dogs (Arii et al., 2006; Blakeslee et al., 1885). However, many experiments particularly the in vivo analysis experiments should be performed before it`s clinical applications.

CHV genome was constructed as a BAC by Arii et al., 2006. Most of the reported recombinant CHVs have utilized HR, which is technically problematic, laborious, time-consuming, and needs multiple rounds of recombinant viruses purification which requires more technical skills.

TK deleted mutants in recombinant CHV has been predicted to have low-level pathogenicity. Although gancyclovir and acyclovir primarily target the *TK* gene (Drew and Erlich, 2008; Topalis et al., 2018), their effects on CHV need to be elucidated and clarified. These types of drugs could be administered if CHV vectors are applied for animal gene therapy but trigger side effects. In terms of using CHV vectors for several gene therapy applications in companion animals, the CHV infectious clone including *TK* gene could be generated (Strive et al., 2007).

CHV had also been developed as a viral vector for European red foxes vaccination. However, there were some obstacles as the absence of humoral response to the inserted foreign genes beside the attenuation of the used viral vector (Strive et al., 2007). One possible explanation of this attenuation is the inactivation of the *TK* gene with an excess of the foreign genetic material in the recombinant viral vector genome. To overcome attenuation in foxes, improved CHV BAC vector system has been developed. Another alternate insertion site for foreign

Table 1
Herpesviruses of dogs, cats, and pigs carrying several foreign immunogenic genes to protect against several important diseases; agent. targeted genes, immunization, and their responses.

Viral vector	Agent	Target	Immunization	Response	References
Canine herpesvirus (CHV)	Neospora caninum	NcSRS2	Dogs	IgG antibody to N. caninum	(Nishikawa et al., 2000)
	Rabies virus	G protein	Dogs	Protective neutralizing antibodies (NA)	(Xuan et al., 1998b)
	Agent	Target	Immunization	Response	References
Feline herpesvirus (FHV-1)	Rabies	Glycoprotein (G) of rabies virus	Cats	Protective VNA and the vaccinated cats were protected during the challenge	(Chen et al., 2019)
	Toxoplasma gondii	ROP2 antigen	Cats	IgG	(Mishima et al., 2002)
	Feline leukemia virus (FeLV)	Envelope glycoprotein gene	Cats	Partial protection	(Willemse et al., 1996)
	Feline immunodeficiency virus (FIV)	Gag protein	–	–	(Sato et al., 2001)
	Feline calicivirus (FCV)	Precursor capsid gene	Cats	Complete Protection	(Yokoyama et al., 1998)
	Agent	Target	Immunization	Response	References
Pseudorabies virus	PRRS	GP5-M	Mouse then piglets	NA and lymphocyte proliferative responses	(Jiang et al., 2007)
	Foot and mouth disease virus (FMDV)	P1 gene	Pigs	Humoral and cellular immune responses with incomplete protection	(Li et al., 2008)
		P1 and multiepitope gene“FHG” consisting of 6 B cell epitopes and two T cell epitopes of FMDV	Pigs	Enhanced immunogenicity Need further studies	(He et al., 2008)
		VP1	Pigs	Non- protective	(Qian et al., 2004)
		FMDV and PPV	Mouse	Neutralization activity in mice	(Hong et al., 2007)
	Porcine circovirus type 2	ORF2	Piglets	Lymphocyte proliferation response and antibodies (Abs)	(Song et al., 2007; Zheng et al., 2015)
		ORF1 and partial *ORF*2 gene	Balb/c mice	Lymphocyte proliferation response and Abs	(Ju et al., 2005)
	Hog cholera virus	Glycoprotein E1	Pig	Complete protection	(van Zijl et al., 1991)
	Japanese encephalitis virus	NS1 gene	Balb/c mice, Pig, and pregnant sows	Protective	(Qian et al., 2015; Xu et al., 2004)
		Premembrane (prM) and envelope (E) proteins SX09S-01 strain	Mouse	Abs	(Xu et al., 2004)
	CSFV	*E* 2 gene	Pigs	Complete protection	(Wang et al., 2015)
	Schistosoma japonicum	Sj26GST and SjFABP	Mice and sheep	Partial protection	(Wei et al., 2010)
	H3N2 subtype swine influenza virus (SIV)	Haemagglutinin (HA)	Mice	Protective	(Tian et al., 2006)
	Swine-origin H1N1 influenza A	HA gene	Pigs	Protective during challenge	(Klingbeil et al., 2015, 2014)
	Porcine parvovirus (PPV)	VP2	Piglets	Complete protection	(Chen et al., 2011)
	Transmissible gastroenteritis virus	*S* gene	–	–	(Yin et al., 2007)
	T. gondii	TgSAG1	Mice	Partial protection	(Liu et al., 2008)
	Rabies virus	rgp	Dogs	Immune response	(Yuan et al., 2008)

sequences is the guanine/cytosine (GC)-rich UL21-UL22 intergenic region, which is a non-essential region for the growth (Strive et al., 2007). It could be replaced with a marker gene without affecting *TK* gene leaving it intact. The generation of recombinant CHV constructs has been publicized in few reports as a recombinant to *Neospora caninum* surface protein (NcSRS2), PRV gB, foreign genes utilizing a lacZ-*TK* gene cassette and rabies virus G protein (Nishikawa et al., 2000, 1999; Rémond et al., 1996; Xuan et al., 1998a, b) as summarized in Table 1.

3.2. Feline herpesvirus

Feline herpesvirus type 1 (FHV-1) is one of the major pathogens causing upper respiratory tract infection, known as feline viral rhinotracheitis (FVR) in cats. The infection is more severe and generalized in immune-compromised cats, especially newly born or debilitated cats resulting in a high rate of mortality (Munks et al., 2017; Povey, 1979). Successful reduction in disease incidence was achieved through extensive vaccinations by modified live or inactivated FVR vaccines on a large scale (Bittle and Rubic, 1975; Povey, 1978; Summers et al., 2017). Genetic engineering is used to delete the genes involved in FHV-1 pathogenicity to construct what is called genetically engineered FHV-1. These genetically engineered FHV-1 established their efficacy as live vectors in vaccine development for FVR and are easily to be distinguished from wild strains by a clear genetic marker (Willemse et al., 1994; Yokoyama et al., 1996b). Three areas in the FHV-1 were found to be associated with their virulence; gI homologous gene, ORF2 downstream of the gC homologue, and *TK* gene. The *TK* gene had been as well used a target site for insertion of a foreign DNA during the development of recombinant vaccines (Cole et al., 1990; Tai et al., 2016; Wardley et al., 1992). A recombinant FHV-1 can deliver several foreign genes of many infectious agents such as feline calicivirus (FCV) (Yokoyama et al., 1996a), feline leukemia virus (FeLV) (Willemse et al., 1996), toxoplasma gondii (Mishima et al., 2002), rabies (Chen et al., 2019) and feline immunodeficiency virus (FIV) (Sato et al., 2001) as summarized in Table 1.

3.3. Pseudorabies

Porcine pseudorabies virus (PRV) belongs to genus Varicellovirus in the subfamily Alphaherpesvirinae in the Herpesviridae family. PRV induces respiratory complications, nervous manifestations, abortions with grievous economic outcomes (Nauwynck et al., 2007; Wong et al., 2019). Its genomic DNA is a linear with an approximate 150 kb. It possess many propitious features making it a promising viral vector candidate such as : (1) the clear genetic background (2) a stable well defined genomic structure (3) the stability of the virus and its replication are not hampered by stable expression of gene of interest (4) the presence of many ideal convenient insertion sites in the large DNA genome and several advantageous strong promoters have also been known and (5) the ability to infect a wide arrays of hosts without infecting or threatening humans (Klupp et al., 2004; Qian et al., 2004; Thomsen et al., 1987; Wei et al., 2017).

TK, gI, PK, gG and gE genes constitute insertion sites for the gene of interests. All of them are not required or necessary for virus replication (Klupp et al., 2004; Olsen et al., 2006). Inactivation, deletion or even replacement of one or more of these genes with heterogeneous genes results in their attenuation with no effect on PRV replication (Dong et al., 2014; Kimman et al., 1992; Szpara et al., 2011), making it advantageous as a live marker vaccine. Based on its attenuation, PRV is proven to be an ideal candidate as a live virus vector to protect against both PRV and other infectious diseases. According to the data delivered by several previous studies (Dong et al., 2013; Genmei et al., 2011; Wang et al., 2013; Zhang et al., 2013), vaccines carrying a protective antigen material together with a cytokine(s) provoke stronger immunity than the antigen alone. As an example a recombinant PRV, without the gG protein, has been generated co-expressing IL-18 and PCV2 capsid protein (Gracie et al., 2003; Zheng et al., 2015). This vaccine was very efficacious as it could raise the protective immunity in mice due to the effect of the multifunctional cytokine that increases both innate and acquired immunity, and potentiates Th1 and Th2 immune responses (Gracie et al., 2003; Zheng et al., 2015). PRV protects against various infectious agents causing diseases in swine and also in mice as foot and mouth disease virus (Kamel et al., 2019; Li et al., 2008), porcine circovirus type 2 (Song et al., 2007; Zheng et al., 2015), hog cholera (van Zijl et al., 1991), japanese encephalitis (Qian et al., 2015; Xu et al., 2004), transmissible gastroenteritis virus (Yin et al., 2007), *Brucella melitensis* in mice (Yao et al., 2015), rabies virus (Yuan et al., 2008), *T. gondii* (Liu et al., 2008), porcine parvovirus (Chen et al., 2011), H1N1 influenza A virus of swine source (Klingbeil et al., 2015, 2014), H3N2 subtype swine influenza virus (SIV) (Tian et al., 2006), *Schistosoma japonicum* (Wei et al., 2010), classical swine fever virus (Wang et al., 2015) and porcine reproductive and respiratory syndrome virus (PRRS) (Jiang et al., 2007). Their immunization efficacy and responses are listed in Table 1.

3.4. Bovine herpesvirus type 1 (BHV-1)

BHV-1 represents an important bovine pathogen with a high prevalence rate. It affects the reproductive system and respiratory tract inducing rhinotracheitis and conjunctivitis (Muylkens et al., 2007). There are many unique advantages for employing BHV-1 as a viral vector among other vectors. The attenuated BHV-1 strains are extensively available as well as the basis of attenuation has been established and best-known (Ren et al., 2009b). Because of the regular immunization in cattle against BHV-1, the used vaccines must be completely safe for humans and cattle and would preclude the necessity for an extra-vaccination toward BHV-1(Ren et al., 2009b). All these features favor BHV-1 as an attractive live vaccine vector candidate for protection against different bovine diseases.

Recombinant BHV-1 conveying bovine pathogen foreign genes have already been promulgated to protect against BHV-1 and other infectious diseases as shown in the Table 2 (Kamel et al., 2019; Kit et al., 1991; Wang et al., 2003). As examples, FMD and BRSV will be underlined. With respect to FMD (Ren et al., 2009a), BHV-1/ gE-/VP1 recombinant vaccine had been generated for FMD and IBR protection. The recombinant BHV-1 expressing BRSV F protein has been displayed to be a more suitable vaccine candidate inducing neutralizing antibodies in the calf against BRSV (Furze et al., 1997; Taylor et al., 1997).

3.5. Bovine herpesvirus 4 (BHV-4)

Bovine herpesvirus 4 (BoHV-4), Rhadinovirus genus belonging to Herpesviridae family, has been globally recovered from both healthy and clinically diseased cattle (Donofrio et al., 2007a; Thiry et al., 1989; Zimmermann et al., 2001). Although the tropism of BoHV-4 is directed toward bovine endometrial cells, its role in pathogenicity remains unclear (Donofrio et al., 2007a). A limited number of researchers could experimentally reproduce the disease (Thiry et al., 1989). BoHV-4, unlike most herpesviruses, can infect and replicate in a wide array of host species in vivo and in vitro as chickens (Barahona et al., 1973; Bartha et al., 1965; Donofrio et al., 2002). Rare infections were reported in lions, owl monkeys and cats (Bublot et al., 1991). BoHV-4 has been experimentally displayed to infect goats (Moreno-Lopez et al., 1989), rabbits and guinea pigs (Egyed et al., 1997). The feasibility of utilizing a BoHV-4 based vector in chickens for vaccination purposes is also very important as it is non-pathogenic even if administrated in high doses. Their application as a heterologous viral vector is to overcome the disadvantage of using homologous vector viruses that some of them neutralized by the maternal Abs (Donofrio et al., 2008a). Albeit BoHV-4 is a gammaherpesvirus based on its genome sequence (McGeoch et al., 2005), it has essential biological properties differ from other gammaherpesviridae members. One of them is that there is no warranty for

Table 2
Herpesviruses of ruminants and equine carrying several foreign immunogenic genes to protect against several important diseases; agent. targeted genes, immunization, and their responses.

	Agent	Target	Immunization	Response	References
Bovine herpesvirus type 1 (BHV-1)	FMDV	Capsid protein (VPI) epitope	Calves	Protective Ab level	(Kit et al., 1991)
	FMDV	VP1 gene	Rabbit	Abs	(Ren et al., 2009a)
	Bovine respiratory syncytial virus	Synthetic G gene	Calves	Partial protection Abs and lymphocyte proliferation response	(Taylor et al., 1998)
	Bovine viral diarrhea virus	Glycoprotein E2	–	–	(Schmitt et al., 1999)
	Mannheimia haemolytica	The viral Glycoprotein C gene with a leukotoxin-plpE chimeric gene	Bighorn sheep (BHS)	Triggered antibodies could not protect BHS during *M. haemolytica* challenge	(Batra et al., 2017)
	Agent	Target	Immunization	Response	References
Bovine herpesvirus 4	Caprine herpesvirus type 1 (CpHV-1)	gD	Goats	Full protection	(Donofrio et al., 2013)
	Peste des Petits Ruminants Virus	Hemagglutinin (H) glycoprotein	Immunocompetent C57BL/6 mice	Cellular and humoral immune responses specifically T cell, cytotoxic T lymphocyte, and serum neutralizing antibody against PPRV	(Macchi et al., 2018)
	Bluetongue virus	VP2 provided by a heterologous signal peptide to its N terminus and a transmembrane domain to its c-terminus	Mice	Serum neutralizing Abs	(Franceschi et al., 2011)
	Bovine viral diarrhea virus (BVDV)	The (gE2-14) putative transmembrane domain was removed and a 14 amino acids peptide was added to its c-terminus and an Ig K signal peptide to N terminus	Rabbits and sheep	Serum neutralized antibodies	(Donofrio et al., 2007b)
	Monkeypox virus (MPXV)	MPXV glycoproteins, A29 L, M1R and B6R	STAT1 knockout mice	Complete protection	(Franceschi et al., 2015)
	Ebola virus (EBOV)	Synthetic EBOV glycoprotein (GP) gene	Goats	Long-lasting anti-EBOV antibodies are provoked	(Rosamilia et al., 2016)
	Agent	Target	Immunization	Response	References
Equine herpes virus	Swine influenza virus (H1N1)	H1	Pigs	Abs and incomplete protection	(Said et al., 2013)
	Bluetongue virus	VP5 & VP2	Mice	Abs and full protection	(Ma et al., 2012)
	Bovine viral diarrhea virus (BVDV)	Tructural proteins (E1, E2, C, E^{rns})	Cattle	NA response diminished viremia levels and declined virus shedding from the nostril	(Rosas et al., 2007a)
	West Nile virus	E & prM proteins	Horses	Specific IgG(T) to E-protein-, NA, and IgGb,	(Rosas et al., 2007b)
	Venezuelan equine encephalitis virus	Structural proteins	Mice	Full protection	(Rosas et al., 2008b)
	Canine influenza virus (CIV)	H3	Dogs & Mice	Abs (Mice and dogs) Dogs were protected against clinical symptoms	(Rosas et al., 2008a)
	Canine distemper virus (CDV)	H & N protein	Pups	High NA. levels EHV-H and EHV-H&EHV-N (pups were protected clinically during the challenge) but in the EHV-N group pups manifested moderate signs	(Pan et al., 2017)
	Rift Valley fever (RVF) virus	Gc & Gn	Sheep	Protection titers were provoked at day 49 post-vaccination	(Said et al., 2017)
	Schmallenberg virus (SBV)	Gc domain of the SBV	Cattle	Protect two of four animals	(Wernike et al., 2018)

growth transformation or oncogenicity caused by BoHV-4. BoHV-4 could accommodate large sizeable foreign genes inside its genome without any noticeable deleterious impact on its replication. Because of these features, it has been introduced as a viral vector for cancer therapy and gene delivery (Donofrio et al., 2006, 2009; Donofrio et al., 2013, 2008b; Donofrio et al., 2007b, 2011; Redaelli et al., 2012; Rosamilia et al., 2016) as presented in Table 2. L1.7 gene had been thought as an attractive targeting site for the insertion of a heterologous antigen expression cassette resulting in viral vector attenuation (Capocefalo et al., 2013).

3.6. Equine herpesvirus

The EHV-1 strain RacH was constructed as BAC (Rudolph et al., 2002) to be used as a worldwide live vector. Its most important outstanding features is its capability to enter extensive arrays of cell types originated from varied sources (Trapp et al., 2005). Its safety was demonstrated in equine species and many different species. Its attenuation was issued to the deletion of both copies of gene 67 in addition to other modifications and alterations in its genome (Hübert et al., 1996; Neubauer et al., 1999; Osterrieder et al., 1996).

Previous work demonstrated the stability and efficiency of several foreign genes in inducing both cellular and antibody immune response. The response was enough to protect the challenged animals from different animal species including non-equine species as mice, cattle and dogs (Ma et al., 2012; Rosas et al., 2006, 2007a; Rosas et al., 2008b, b; Said et al., 2011, 2013). The lack of pre-existing immunity toward EHV-1 within non-equine species is a merit of these vaccines which bypass interference of immunity with the vector itself. Another advantage is the absence of cross-reaction between triggered NA during vaccination with EHV-1 delivering bovine viral diarrhea and BHV-1 which is very important for the diagnostics and molecular epidemiologists. (Table 2)

3.7. Herpesvirus of turkey (HVT)

Herpesvirus of turkey (HVT), a member of the genus Mardivirus and non- pathogenic alphaherpesvirus, was initially isolated from domesticated turkeys (Baigent et al., 2006; Ingrao et al., 2017). The virus has an antigenic and genetic relationship with MDV which causes chicken Marek's disease (Calnek, 2001; Fauquet et al., 2005; Gimeno et al., 2016). MDV infection leads to the development of T-cell lymphomas and infiltration in peripheral nerves within weeks after the infection (Calnek, 2001). These likenesses have assisted in vaccination tactics as HVT vaccination has triggered durable, and protective immunity against Marek's disease in chickens (Gimeno et al., 2016). Vaccinations with HVT have significantly shown to reduce Marek's disease (MD)-related losses and also prevention of MD (Gimeno et al., 2016).

HVT is an efficient delivery system for several immunogenic genes that help in controlling multiple poultry diseases (Table 3). It has some attractive features: (1) It is a non-pathogenic persistent infectious agent for chickens which results in continual immune response keeping the protective antibody titer levels augmented, (2) HVT vaccine can resist long-term storage and transport due to its availability in lyophilized form (Reddy et al., 1996; Witter et al., 1970) and (3) HVT genome is large enough to accommodate insertion of several multiple foreign genes. Recombinant HVT (rHVT) vaccine is considered one of the beneficial viral vectors against several poultry disease-associated viruses through targeted gene expression (Ingrao et al., 2017; Rauw et al., 2010; Reddy et al., 1996).

Generally, the nonessential' genes delineated in some alphaherpesviruses for the replication and growth and consequently, their respective gene products are commonly the targets for inserting foreign gene during designing alphaherpesvirus vectors (Faust et al., 2002; Morgan et al., 1992). The US1, US2, US10, and TK genes were defined as 'non-essential' genes for herpesviruses' growth in cell cultures (Andoh et al., 2017; Bacon and Witter, 1992; Morgan et al., 1993; Rauw et al., 2010). Recombinant HVT or MDV in US2 and US10 insertion sites have been constructed. Following their vaccination, full protection has been conferred against very virulent Marek's disease virus (vvMDV) challenge and partial protection was provoked against virulent IBDV as obtained by Tsukamoto et al. (1999) who constructed a recombinant vaccine expressing infectious bursal disease virus VP2 at US2 insertion site (Tsukamoto et al., 1999). HVT-BAC clones were constructed by using US2 site as an insertion region and conferred full protection against the challenge with virulent Marek's disease virus (vMDV) (Baigent et al., 2006).

On the other hand, another insertion site (US10) had been used for NDV F protein, conferred nearly 90% protection against vNDV and protected effectively against vvMDV as shown by several studies (Morgan et al., 1992; Sakaguchi et al., 1998). Insertion sites gene loci (US2 and US10) for foreign genes did not hinder the recombinant virus replication in vivo (Cantello et al., 1991; Morgan et al., 1992; Parcells et al., 1994). Gao et al (2011) demonstrated that US2 insertion site for AIV HA gene provided more effective protection than rHVT delivering the AIV HA gene at the US10 locus.

MDV, a herpesviridae family member, is considered an oncogenic alphaherpesvirus that causes T-cell lymphoma in chicken. The three known serotypes of MDV: serotype 1 involves all pathogenic oncogenic strains; serotype 2 contains natural strains that are non-pathogenic to chickens; and serotype 3 contains HVT, a non-oncogenic, MDV-related virus isolated from turkeys (Bülow and Biggs, 1975; Cao et al., 2015; Schat, 2016; Witter et al., 1970). The insertion sites that can be used to express foreign genes of other microbes include the *meq, US10, US3* genes and the interface region between unique short and short inverted

Table 3
Poultry herpesviruses (HVT and MDV) carrying several foreign immunogenic genes to protect against several important diseases; agent targeted genes, immunization, and their responses. The commercially viral vectors are also included.

Agent or disease	Target	Immunization	Response	References
Coccidiosis	Ea1A gene	Chickens	–	(Vermeulen, 1998)
H7N1 avian influenza virus	HA	Chicken	Complete protection	(Li et al., 2011a)
Chlamydia psittaci	pmpD-N	One-day-old SPF chickens	Partial protection and decrease the clinical signs	(Liu et al., 2015)
A clade 2.2 H5N1 strain (A/swan/ Hungary/4999/2006)	Hemagglutinin (HA) gene	Chicken	Protection during challenge with an adjuvanted live vaccine at day-old	(Kapczynski et al., 2015)
Newcastle disease	F gene	Day-old chicks	Complete protection	(Esaki et al., 2013)
Infectious bursal disease	VP2	In ovo or by the subcutaneous route, to 1-day-old chicks	Full protection	(Bublot et al., 2007; Darteil et al., 1995)
Laryngotracheitis virus	Glycoprotein B	SPF layer chicken Broiler chickens	(92%-100%) protection 67% and 87% did not develop clinical signs	(Esaki et al., 2013; Godoy et al., 2013)
Low pathogenic avian influenza virus (LPAIV) H9N2	HA and neuraminidase gene (NA)	–	–	(Zhang et al., 2014)

repeats (Lupiani et al., 2004; Sakaguchi et al., 1994, 1993; Sonoda et al., 1996). MDV vaccines are practically the only vaccine that could be inoculated into day-old chicks and cannot be neutralized even by high maternal antibodies titer level because MDVs are less affected by maternal antibodies than other virus vaccines. The featured immunity generated by MDV vaccine is long-lasting throughout chickens' lives (Li et al., 2016; Venugopal, 2000).

A molecular clone of a vvMDV field strain GX0101 and its meq-deletion mutants were constructed (Li et al., 2011b; Sun et al., 2009). The deletion of the meq from a very virulent GX0101 mutant leads to the loss of its pathogenicity and moreover provided a superior protective immunity than CVI988/Rispens in chickens during vvMDV challenge (Su et al., 2010). Furthermore, the generated a meq-deleted Md5 strain of MDV based on cosmid system also displayed superior protective immune response than CVI988/Rispens in chickens during their challenge with a very virulent plus MDV field strain (vv + MDV), Md5 (Lee et al., 2012, 2010; Lee et al., 2008, 2011).

Zhang and his team could steadily express LPAIV-H9N2 strain H9N2 HA and NA via generating a recombinant MDV carrying these two genes as two separated transcription units lacking meq oncogene by using both MDV-BAC system and the combining Red/ET with FLP/FRT recombinant technology (Zhang et al., 2014). Several recombinant HVT are listed in Table 4.

The vaccine VaxxitexR HVT + IBD has been licensed and certified to be used as a commercial animal herpesvirus vector vaccine product. Recently, several recombinant MDV vaccines have been constructed, and some of them expressing foreign gene have conferred a good protective immunity in chickens (Sonoda et al., 2000; Tsukamoto et al., 1999). Several other commercial vaccines are tabulated in Table 5.

4. Aims to improve the quality of the recombinant vaccine

- We can screen and detect the genes that are not essential in virus replication and whether their deletion can boost cell-mediated and humoral immune response since the existence of these genes results in minimizing the immune response or downregulating MHC-I and MHC-II that represent viral peptide to APC
- Enhancing the expression of genes of interest can be achieved through viral promoter's identification in addition to the usage of different viral promoters to accelerate and strengthen foreign gene expression.
  Some co-stimulatory molecules (cytokines or chemokines) such as interleukins, interferon (IFN)-γ, ICAM-1, LFA-3 molecules and GM-CSF have been reported to be inserted into herpesviruses and poxviruses based recombinant vaccines (García-Arriaza and Esteban, 2014). Their insertion is either via genomic integration of the gene encoding the immunomodulatory under control of a virus promoter or through their exogenous inoculation as soluble molecules in the organism to enhance and provoke more immunity against the diseases.

- Codon-optimized synthetic genes are more likely to provoke more protection when it is used as synthetic genes in the construction of the recombinant viral vector vaccines
- Removal of the genes that lead to evasion from the immune system is also a very crucial issue to be regarded.
- Codon optimization and protein design for maximizing the expression are very critical steps.
- Using the viral vectors with the adjuvant may boost the immune response. Indeed, glycol chitosan, flagellin FljB and ENABL® have increased the potency of adenovirus-based vector vaccines against BoHV-1, rabies, FMD respectively (Barrera et al., 2018; Gogev et al., 2004; Xiao et al., 2017). On the other hand, the all-trans retinoic acid (ATRA) adjuvant has enhanced only the primary not the secondary systemic and mucosal immune responses induced by adenovirus-based vector vaccines (Tuyishime et al., 2014).
- While herpesviruses per se are potent immunogens, the vectors themselves when combined with other antigens act as immunogens.
- Herpesviruses can be used as a booster vaccine to another vaccine type to enhance cellular immune responses against specific antigens or as a priming component combined with a protein as well as an adjuvant to enhance and raise B cell responses through prime/boost (Romanutti et al., 2013).
- Codon pair bias deoptimization or crispr cas9 as a trail for attenuation the highly virulent herpesviruses strains (Tang et al., 2018a).

5. Key issues

- Viral vectors are auspicious vehicles for gene therapy and vaccines.
- Vaccines based on viral vectors can improve immunogenicity and provoke a strong cytotoxic T lymphocyte (CTL) response to get rid of virus-infected cells.
- Novel vaccines based on live vectors may incorporate the trigger of extensive, robust and lasting immune responses with permissible safety profiles.
- The development of herpesviruses viral vectors is facilitated by a better understanding of viral biology, advanced molecular techniques and the relationship between the vector and the immune system.
- Recent developments and approaches of herpesviruses vectors production and purification and successes and failures in their applications to date.

6. Conclusion and perspectives

There is no doubt that recent molecular biology discoveries will lead to better understanding of viral molecular biology and genetics. The use of recent molecular biology tools and techniques to manipulate and insert foreign genes is in progress. The emergence and re-emergence of human and animal diseases that are harder to control and treat represent a threat to human and animal populations. Vaccination, including viral vector vaccine, is one of this intervention to control these diseases. Some immunomodulatory and co-stimulatory molecules will probably enhance the immunogenicity of viral vector vaccines. The use of adjuvants to the recombinant herpesviruses vector may be an outstanding point in the future. The utility of these vaccines for use against human pathogens as well can be considered since the basic design and immune concepts are the same.

Compliance with ethical standards

The authors declare that they have no conflict of interest
This article does not contain any studies with human participants or

Table 4
Commercial poultry herpesviruses (HVT and MDV) viral vectors carrying several foreign immunogenic genes to protect against several important diseases; commercial name with its company names and their insert.

Commercial name (Manufacturer)	Innovax-ND (Merck)	Vectormune ND (Ceva)	Vectormune AI (Ceva)	Vectormune LT (Ceva)	ectormune IBD (Ceva)	Vaxxitek HVT-IBD (Merial)	Innovax-ILT (Merck)
Insert	NDV F	NDV F	AI H5	ILTV gB	IBDV VP2	IBDV VP2	ILTV gI & gD

animals performed by any of the authors.

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