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Pox virus as Vectors for Recombinant Vaccines Development

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Abstract

Poxviruses are big viruses with complex DNA genomes that belong to the Poxviridae family. The family includes several pox viruses of medical and veterinary importance. In 1980, the small pox was eradicated globally with an intensive mass-vaccination campaign with a highly efficacious live vaccine of another pox virus called the vaccinia virus. Despite the eradication of smallpox, there was an explosion of interest in vaccinia virus in the eighties. This interest has stemmed in part from the application of molecular genetics to clone and express foreign genes from recombinant vaccinia viruses. Thus, the current paper provides a review of the pox virus as a vaccine vector and a possible application of a pox virus-based vector. The poxvirus recombinants that have been generated for vaccination against heterologous pathogens includes, (i) the engineering of the Copenhagen strain of vaccinia virus to express the rabies virus glycoprotein. (ii) A fowl pox-based recombinant expressing the Newcastle disease virus fusion and hemagglutinin glycoprotein has been shown to protect commercial broiler chickens for their lifetime. (iii) Recombinants of canary pox virus, which is restricted for replication to avian species, have provided protection against rabies virus challenge in cats and dogs, against canine distemper virus, feline leukemia virus, and equine influenza virus disease. In humans, canarypox virus-based recombinants expressing antigens from rabies virus, Japanese encephalitis virus, and HIV have been shown to be safe and immunogenic. (iv) A highly attenuated vaccinia derivative, NYVAC, has been engineered to express antigens from both animal and human pathogens. It is recommended that the application of multiple recombinant viruses in research and vaccinology has led to the development of poxvirus vectored vaccines which have proved to be even safer and more efficacious non-replicating vectors used to eliminate serious pathogens when used on the target species.

Keywords: Pox virus, Recombinant viruses, Vaccine, Vector

Introduction

Poxviruses are one of the most widely investigated vectors for gene delivery in the context of stimulating innate and adaptive immunity with recombinant vaccines (Philip *et al*., 2005). Dr. Edward Jenner demonstrated in 1798 that deliberately inoculating humans with cowpox virus provided protection against the antigenically related smallpox virus (variola) (Pastoret and Vanderplasschen, 2003). This discovery led to the eradication of small pox from the earth in 1980 after a world-wide vaccination campaign with the vaccinia virus vector (Fenner *et al*., 1988; Vanderplasschen *et al*., 2003). Since then, numerous reports have described the usefulness of this vector system, particularly with respect to developing vector-based vaccine candidates (Bhanuprakash *et al*., 2016). Thus, by splicing genes from heterologous pathogens into the vaccinia virus vector, one could immunize against that cognate pathogen (Gillard *et al*., 2011).

Vaccinia virus is the prototypical poxvirus and has been administered to more than a billion people, largely through the highly successful smallpox eradication program (Philip *et al*., 2005; Fenner *et al*., 1988). The large size of the vaccinia genome and the stability of recombinant vectors have allowed multiple transgenes to be expressed in a single vaccinia virus vector (Garcel *et al*., 2007).Another major advantage is that proteins expressed by vaccinia virus tend to be more immunogenic than the native protein, most likely secondary to the inflammatory response triggered against highly immunogenic vaccinia proteins (Bertram *et al*., 2009).Other advantages of poxviruses include a wide host range, accurate replication potential, and efficient post-translational processing of inserted gene products (Verardi *et al*., 2012).

Currently, numerous strains of vaccinia have been engineered to express a wide range of antigens from a wide range of bacterial, viral, and parasitic pathogens, with the recombinants being tested in both animal models and target species (Qin *et al*., 2015; Qin *et al*., 2011; Carroll *et al*., 2011). Initial safety concerns of vaccinia virus vectors have been addressed by the use of highly attenuated replication-deficient strains of the virus as well as the engineering of host range-restricted pox viruses such as canary pox virus that, while restricted for productive replication to avian species, have been shown to effectively vaccinate non avian targets (Walsh and Dolin, 2011; Bertram *et al*., 2009; Jacqueline *et al*., 2009). The initial studies on vaccinia virus were extended to other members of the pox virus family so as to provide species specific vectors (Stading *et al*., 2016; McFadden, 2005).

Fowl pox-based vectors are an example of recombinant vaccines used in the poultry industry. Much information has been gained through this period, and today some commercial success has been evidenced by the licensing of several products in the veterinary area (Elmich *et al*., 2006; Vanniasinkam *et al*., 2021). Recombinant DNA technology transformed molecular biology in the early 1980s, allowing foreign DNA to be inserted into poxvirus genomes (Sampedro *et al*., 2015). In 1960, Woodroffe and Fenner reported that homologous recombination between the genomes of two replicating poxviruses could occur (Woodroofe and Fenner, 1960). The capacity to insert heterologous genes into poxvirus genomes greatly enhances their vaccination potential (Juan and Mariano, 2014). Rather than small pox vaccines, vaccinations against a variety of heterologous diseases, including the hepatitis B surface antigen (Margaret, 2010), influenza virus hemagglutinin (Gerd and Caroline, 2003), herpes virus glycoprotein D and rabies virus glycoprotein. In addition to continuing research in this field for vaccinations, pox virus-based vectors immunotherapy is being developed today and new fields of endeavor are being investigated, such as in cancer (John and Thomas, 2002; Rauch *et al*., 2018; Zilinget *al*., 2021).

The aim of this review was to bring together available data from primary research conducted so far onpox virus-based vectors as recombinant vaccines and their possible application of a pox virus based vector.

Background of pox virus

Poxviruses are big viruses with complex DNA genomes ranging in size from 130 to 300 kb pairs, each end featuring a hairpin loop (Souza *et al*., 2005). Therefore, mammalian poxvirus genomes are around 130 kb, and avian poxvirus genomes are around 300 kb. Because of the huge genome size, more than 10 kb of foreign DNA can be inserted without impacting infectivity or other key viral functions (Kim *et al.*, 2012). Poxviruses, unlike other DNA viruses, have their own transcription machinery, viral DNA-dependent RNA polymerase, and post-transcriptional modifying enzymes, allowing them to self-replicate in the cytoplasm (Choi *et al*., 2013).
The Poxviridae family is divided into two subfamilies, one of which, Chordopoxviridae, contains vertebrate poxviruses (Barrett *et al*., 2008). The Chordopoxviridae contains eight genera that may infect vertebrates; the Orthopoxvirus and Avipoxvirus genera have been extensively developed for use as recombinant vectors in vaccine development (Souza *et al*., 2005). Variola virus, which causes smallpox, and vaccinia virus, which is used in the smallpox vaccine, are both members of the Orthopoxvirus genus, while fowlpox and canarypox are both members of the Avipoxvirus genus (Hendrickson *et al*., 2010).

Poxviruses are excellent as vaccine vectors because of certain properties. Importantly, these vectors are extremely stable and can be stored and used for up to two months after being lyophilized (Haut *et al*., 2005). They are inexpensive to produce and have the ability to be administered in a variety of ways, as evidenced by their safe delivery via intradermal, intranasal, intravaginal, and intrarectal routes to induce antibody and T-cell responses (Wang *et al*., 2015). Both mucosal and systemic immune responses to vaccinia recombinants have been observed after oral treatment (Gherardi and Esteban, 1999).

Finally, due to the compartmentalization of the systemic and mucosal immune systems, preexisting immunity to vaccinia virus, one of the fundamental limitations of recombinant-viral vaccines, can be overcome by mucosal vaccination with vaccinia vectors (Robinson and H.L., 2002).

Recombinant poxvirus vector development strategies

The exchange of nucleotide sequences between two similar or identical DNA molecules is known as homologous recombination (Cooper *et al*., 2000). For the creation of recombinant poxviruses, homologous recombination is currently routinely exploited (Moss and B., 2013). This method necessitates the creation of a transfer plasmid (recombination plasmid) carrying the foreign gene insert (heterologous gene) as well as the parent poxvirus genome's left and right homology DNA sequences flanking the insertion site(Bartuli *et al*., 2022) (Fig 1). In order to achieve homologous recombination and recombinant poxvirus formation, permissive cells are infected with the parent poxvirus and then transfected with the recombination plasmid (infection/transfection) (Wyatt *et al*., 2017). Homologous recombination between the parental virus and the recombination plasmid occurs within infected and transfected cells, resulting in a new chimeric recombinant poxvirus. Multiple rounds of limiting dilution and/or plaque assay are used to purify the recombinant poxvirus (Qin and Evans, 2014).

To achieve homologous recombination, numerous criteria must be taken into account, including homology length and DNA structure (Yao *et al*., 2001). When homologous flanks with at least 100–350 bp and linear plasmid DNA were employed in infection/transfection assays with VACV, higher recombination frequencies were found (del Rio *et al*., 2019).The following criteria must be addressed while designing and producing poxvirus-based vectors, in addition to the insertion site and homology length(Mastrangelo *et al*., 2000; Yao *et al*., 2001):

A. The promoters. Selection of the promoter that will drive expression of the heterologous gene is a vital part in the design of poxvirus vectors, given

the temporal regulation of poxvirus gene transcription (early, intermediate, and late) (Knutson *et al*., 2006). In general, promoters with both early and late activity are advantageous for foreign gene expression because they drive heterologous gene production throughout the vector infection cycle, encouraging persistent antigen expression and subsequent immune system stimulation (Buchschacher*et al*., 2000). When the poxvirus vector is replication deficient or when the vector is to be employed in a non-permissive animal species, early promoters are preferred because late promoters, which occur after virus replication, prevent expression(McFadden and G., 2005). The native VACV early/late promoters, the modified early promoter, or synthetic promoters, for which expression has been improved by mutagenesis, are the most often employed promoters to drive expression of heterologous genes by poxviruses (Garca-Arriaza *et al*., 2014).

B. Termination signal. The inclusion of the poxvirus early termination signal within the sequence of heterologous genes may result in premature transcription termination, resulting in low expression levels or the expression of a truncated protein (Joshi *et al*., 2021). Before putting the gene into the vector, termination signals should be eliminated from the heterologous gene sequence using site-directed mutagenesis or synthetic biology (Yoshikawa *et al*., 2015).

C. Codon optimization. Codon optimization of the heterologous gene may aid in achieving higher expression levels, particularly in non-target animal species where replication and late gene expression are compromised. Codon optimization improves recombinant vector stability by deleting unwanted sequences (Norkiene and Gedvilaite, 2012). It can also be used to create multivalent heterosubtypic viral vectors that contain two or more viral genes from closely related virus strains (Vrba *et al.*, 2020). By minimizing or reducing the probability of intramolecular homologous recombination, codon optimization and modifications in the nucleotide sequence of one of the genes improve the vector's stability(Atkinson *et al*., 2010).

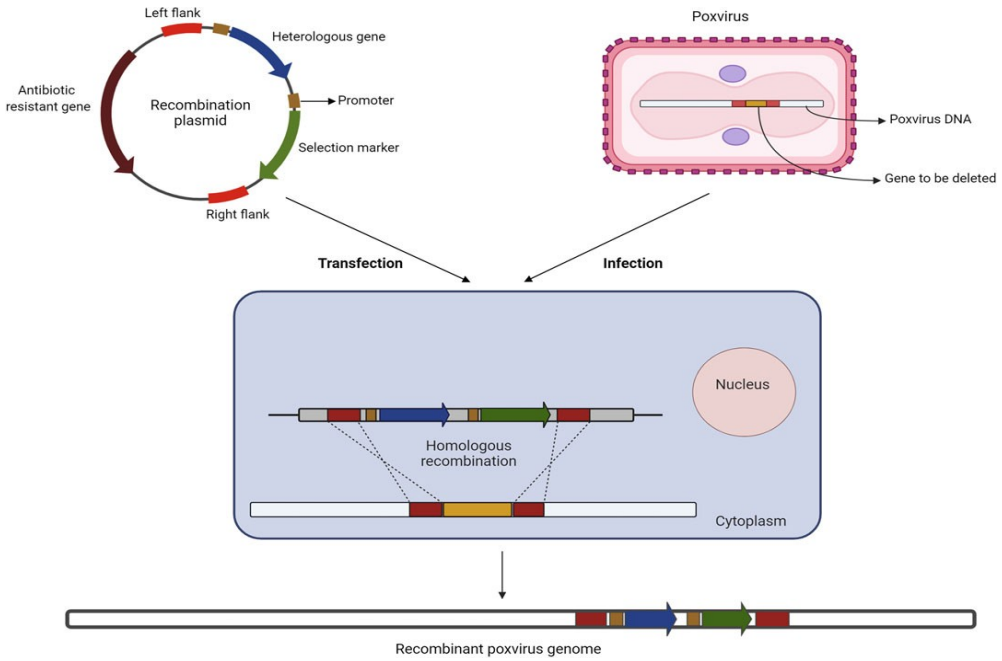

Figure 1: Schematic representation of homologous recombination of pox virus
Source:(Vanniasinkam *et al*., 2021).

D. Selection method. It is one of the most time-consuming phases in creating recombinant poxvirus-based vectors. Recently, fluorescent proteins such as the green fluorescent protein (GFP) have been successfully employed in the selection of recombinant poxviruses. Along with the gene of interest, a gene that expresses GFP or another fluorescent protein is added (Wong *et al*., 2011; Leyrer and Mayer, n.d.). The Plaque assay (Hain *et al*., 2016) can be used to identify recombinant poxviruses that express fluorescent protein. Because promoter interference might result in reduced protein expression levels when numerous genes are expressed simultaneously, the presence of marker genes is not always advised. As a result, methods for creating markerless recombinant poxviruses have recently been devised. Real-time PCR or immunofluorescence tests targeting heterologous genes are the easiest ways (Martins *et al*., 2017). More advanced techniques based on Cre/loxP recombination, which permit selection and subsequent removal of marker genes, have also been established and provide an effective means to construct markerless recombinants (Rintoul *et al*., 2011). Yuan *et al.* (2015) presented a marker-free technique for creating vaccinia virus vectors utilizing CRISPR (clustered regularly interspaced short palindromic repeat)-Cas9.

Recombinant pox viruses as vaccine vector

The use of pox virus-based vectors as recombinant vaccines for heterologous bacterial, viral, or parasitic pathogens was the first practical application of this technology, deriving from the fact that vaccinia virus was an established vaccine (Gómez *et al*., 2008).

A. Vaccinia virus

Vaccinia virus (VACV), a large double-stranded DNA virus, is the prototypic and best characterized member of the poxvirus family. Replication and gene expression occur in the cytoplasm of the infected host cell (Dhungel *et al*., 2020).

Some of the characteristics that have made VACV a popular and extensively used vector include:(i) the virus's large genome size (190 kb), which allows for the manipulation of many non-essential genes without affecting virus replication(Guo *et al*., 2004); (ii) the virus's ability to tolerate insertion of up to 25,000 bp of foreign DNA (Smith *et al*., 1983; Jordan *et al*., 2013); (iii) the virus's ability to induce both humoral and cell-mediated immunities (Gherardi*et al*., 1999; Legrand *et al*., 2004); (iv) the simplicity of delivery and efficiency of immunization through various methods (Hickling *et al*., 2011); and (v) the virus's lyophilized stability at room temperature, eliminating the necessity for a cold chain (Collier and L.H., 1955; Ghobadloo, 2014).

A VACV-based vectored rabies vaccine is the first recombinant poxvirus to be licensed for use as a vaccine(Amann *et al*., 2013). A recombinant by introducing the rabies virus (RabV) glycoprotein (G) gene into the thymidine kinase (TK) locus of the Copenhagen strain of vaccinia virus is created (Desmettre *et al*., 1990; Lauer and K., 2016).It has been used to prevent rabies in red foxes in various European nations, as well as coyotes and raccoons in the United States and raccoons in Canada (Weyer *et al*., 2009; Cliquet *et al*., 2004). The vaccination is administered as an oral bait that is disseminated by hand or airplane in the wild habitat of the target species. In foxes, raccoons, and coyotes, this vaccine is safe and efficacious (Maki *et al*., 2017). It's been demonstrated to work in vampire bats, which are a major rabies virus reservoir (Aguilar-Setién *et al*., 2002). When given orally to skunks and dogs, however, it is less effective (Grosenbaugh *et al*., 2007; Rupprecht *et al*., 2005). Furthermore, because it is a live attenuated vaccine, safety concerns about live virus-based vaccines being exposed to non-target species have been highlighted. To find safer alternatives to this vaccine, recombinant MVA, a significantly attenuated VACV strain expressing the RabV G, was created (Weyer*et al*., 2007).

Recombinant VACV vectors producing the rinderpest virus's hemagglutinin (H) and fusion (F) proteins have been created. By introducing the

H or F gene into the TK locus of the VACV Wyeth strain, two vaccinia recombinants were created(Ellis and R.W., 2001).Even when inoculated cattle were challenged with 1000 times the lethal dosage of rinderpest virus, vaccination with either recombinant or a combo of the two recombinants afforded 100 percent protection (Spinageand C.A., 2003). The VACV vector was not transmitted from vaccinated animals to contact animals. Furthermore, calves vaccinated with a mixture of recombinant vectors showed strong immunity, as evidenced by the absence of an amnestic reaction to rinderpest viral challenge (Giavedoni *et al*., 1991; Verardi *et al*., 2002).

Later, using the TK locus of the VACV Copenhagen strain, another VACV-based recombinant expressing H and F genes (v2RVFH) was created.In place of the natural VACV promoter employed in prior creations, a powerful synthetic VACV promoter was used. In comparison to vRVFH, this led to a threefold increase in H and F gene expression (Wyatt *et al*., 2017).In cattle, a dose of 108 PFU administered intramuscularly provided sterilizing immunity for at least 16 months (citeseerx.ist.psu.edu, n.d.).Interestingly, VACV strain Wyeth, which expresses the rinderpest virus's H and F genes (vRVFH), protects goats from the peste des petitsruminants virus (PPRV). Despite vRVFH's inability to produce anti-PPRV neutralizing antibodies, goats were completely protected against PPR (Jones *et al*., 1993; Herbert *et al*., 2014).The protection evoked by this recombinant vector in goats could be due to cell-mediated immunity or non-neutralizing antibodies. Cross-protection for canine distemper virus (CDV) vectored by VACV vectors has also been proven(Welter *et al*., 2000).

B. Avipoxvirus-Based Vectors

Avipoxviruses were first proposed as vaccine delivery vectors for chickens(Boyle and D.B.,2007).The fowlpox virus (FWPV) and canarypox virus (CNPV), which infect domestic chickens and canaries, respectively, have helped us grasp the molecular and biological properties of avipoxviruses (Joshi *et al*., 2021).

The discovery that recombinant FWPV causes an abortive infection in non-avian tissue cellcultures and expresses foreign antigens capable of eliciting an immune response in mammals prompted interest in employing avipoxviruses as vectors for humans and other animals (Investigation of Local South African Avipoxviruses as Potential Vaccine Vectors, 2014).Furthermore, pre-existing immunity to orthopoxviruses has no effect on the immunogenicity of FWPV and canarypox virus (CNPV), indicating that they could be utilized as vectors in people who have been exposed to vaccinia virus or who have been vaccinated against smallpox (Weli*et al*., 2011). As a result, a vast number of avipoxvirus recombinants based on FWPV and CNPV for use in people and animals have been created(Giotis *et al*., 2019).

Fowlpox Virus-Based Vectors

Several avian influenza (AI)-targeting fowlpox virus recombinant constructs have been created (Criado *et al*., 2019). Hemagglutinin-inhibiting (HI) antibodies were produced in hens by a fowlpox virus recombinant expressing the influenza virus HA protein at the TK locus. When chickens were re-immunized, a boost effect was observed (Richard-Mazet *et al*., 2014).Interestingly, birds with very low levels of HI or neutralizing antibodies were protected against AI (Palya *et al*., 2018). The effector mechanism of protection against AI in birds lacking large amounts of HI or neutralizing antibodies has been proposed (Swayne *et al*., 2000). Some recent H5N1 Asian AI isolates, such as A/chicken/South Korea/03 and A/chicken/Vietnam/04, have shown good levels of protection (Bublot *et al*., 2006). Another recombinant FWPV vector that co-expresses HA (H5 subtype) and neuraminidase (N1 subtype) can give hens 100% protection against AI H5N1 infection. Protection was found to be accompanied by significant levels of HA- and N1-specific antibodies (Qiao *et al*., 2003). This recombinant can provide cross protection against H5N1 and H7N1 highly pathogenic avian influenza (HPAI) virus challenges, owing to cross-reactive immunity afforded by the shared

N1 protein between these two HPAI types(Jiao *et al*., 2016).

Canarypox Virus-Based Vectors

Canarypox virus is another avipoxvirus that has been frequently employed as a vaccine vector (CNPV). ALVAC, a highly purified clone of CNPV, is commonly utilized as a vector (Sasso *et al.*, 2020). This clone produced via serial passage of wild-type CNPV for 200 passes in CEF (Hu and N.C., 2010).The CNPV ALVAC vector was used in human clinical trials as an HIV/AIDS vaccine candidate due to its safety and immunogenicity profile (Sampedro *et al*., 2015). ALVAC-AI-H5 (influenza virus), ALVAC-RV (rabies virus), and ALVAC-CDV-H/F (canine distemper virus) are among the ALVAC-based vectored vaccines approved for veterinary use (Poulet *et al*., 2007). In mice, cats, and dogs, canarypox virus recombinants expressing RabV G have been shown to elicit substantial levels of neutralizing antibodies. After challenge infection, the level of protection seen was comparable to that induced by a replication-competent VACV vector (Huang *et al*., 2009).

C. Parapoxvirus-Based Vectors

Orf virus (ORFV) is the type species of the Parapoxvirus genus of the family Poxviridae and infects sheep and goats, often around the mouth, resulting in acute pustular skin lesions (Fleming *et al*., 2017). However, as a vector, the type species parapoxvirus Orf virus (ORFV) has been frequently employed (www.sciencedirect.com, n.d.). ORFV has several characteristics that make it a good candidate vector: (1) its restricted host range (sheep and goats), (2) its ability to induce humoral and cellular immune responses even in non-permissive hosts (Hain*et al*., 2016; Martins *et al*., 2017), (3) its skin tropism and lack of systemic infection, (4) the fact that ORFV induces short-lived ORFV-specific immunity and does not induce neutralizing antibodies, allowing repeated immunizations (Hain*et al*., 2016; Joshi *et al*., 2018), and (5) the virus's immunomodulatory capabilities (Friebe *et al*., 2004). Orf virus contains multiple immunomodulatory proteins (IMPs) that have been widely studied. These include an interleukin-10 homologue (vIL-10) (Fleming *et al*., 2007), a chemokine-binding protein (CBP) (Seet *et al*., 2003), a granulocyte-monocyte colony stimulating factor (GMC-CSF) inhibitor (Deane *et al*., 2000), an interferon resistance gene (VIR), a homologue of vascular endothelial growth factor (VEGF) (Westphal *et al*., 2007),and at least four nuclear factor-kappa (NF-B) signaling pathway inhibitors (Diel *et al*., 2011; Khatiwada *et al*., 2017). Because of the existence of these well-characterized IMPs, ORFV-based vectored vaccines can be rationally engineered (Martins *et al*., 2017).

ORFV strains D1701 and OV IA82 have been investigated as vectors for veterinary use. After serial cell culture passage of an ORFV isolate from sheep in African green monkey kidney cells (Vero cells), the substantially attenuated ORFV strain D1701 was produced (Reguzova *et al*., 2020). This virus is non-pathogenic in sheep and has good cell culture adaptability. Because of additional genomic deletions, ORFV strain D1701 was further attenuated after adaptation in Vero cells. Even in immunosuppressed natural host sheep, this virus, termed D1701-V, is non-pathogenic (Rziha *et al*., 2000). The D1701-V strain has been tested as a vector in both permissive and non-permissive animal species. The VEGF-E locus of D1701-V has been used to insert heterologous genes using the VEGF-E gene's early promoter in most constructions (Schneider *et al*., 2020). In mice, cats, and dogs, the D1701-V recombinant expressing rabies G can generate significant levels of rabies virus-specific neutralizing antibodies (Amann *et al*., 2013).

D. Swinepox Virus-Based Vector

The only member of the Suipoxvirus genus is the swinepox virus (SPV), one of eight genera within the Chordopoxvirinae subfamily of the Poxviridae (Afonso *et al*., 2002). In pigs, swinepox virus is an acute, often mild, infectious disease characterized by skin eruptions that affect only pigs (MSD Veterinary Manual, n.d.). SPV-based recombinant vectored vaccination candidates have

primarily been developed for pigs because of the virus's limited host range (Yuan *et al*., 2018). A recombinant SPV targeting Aujeszky's disease (pseudo rabies virus (PRV)) was one of the first attempts to employ SPV as a vector (Freuling *et al*., 2017). Under the early/late promoter, the PRV gp40 and gp63 genes were introduced into the TK locus of SPV. At 21 days after vaccination, 90% of scarification-vaccinated pigs acquired serum neutralizing antibodies against pseudorabies virus, whereas 100% of intramuscularly vaccinated animals developed neutralizing antibodies (Vanniasinkam *et al*., 2020).

E. Capripoxvirus-Based Vector

Goatpox virus, Sheeppox virus, and Lumpy skin disease virus are all members of the Capripoxvirus genus (LSDV) (Hamdi *et al*., 2020). SPPV infects sheep while GTPV infects goats, with some isolates infecting both. LSDV infects cattle and buffalo (Gelaye *et al*., 2019). Tulman *et al*., (2002) discovered that these three CPV species share 96–97% nucleotide similarity. Because of their high degree of sequence conservation, cross-infection is possible and immunity is demonstrated among the three viruses. Boshra *et al*., (2015) found that an attenuated LSDV lacking an IL-10 gene homologue (ORF005) provides protective immunity in sheep and goats against virulent capripoxvirus (CPV) exposure. According to Teffera *et al*.(2019), an attenuated strain of any capripoxvirus should be able to defend against SPPV, GTPV, and LSDV. It is possible to create multivalent vaccinations against CPV and other ruminant diseases using these viruses as vectors (Caufour *et al*., 2014).

Furthermore, capripoxvirus replication is limited to ruminants, with no evidence of human infections. These characteristics make CPVs ideal candidates for recombinant vectored vaccine development (Shen *et al*., 2011).

Table 1: Summarizes the poxvirus vectored vaccines that are currently licensed and commercially available for use in veterinary medicine.

Vaccine trade name	Target pathogen	Target species	Insert gene	Poxvirus Vector	References
RABORAL V-RG	Rabies	Wildlife Canines	Glycoprotein	Vaccinia Virus	(Desmettre *et al*.,1990;Kieny *et al*., 1984)
ProteqFlu and RecombiTek	Equine influenza	Horses	HA	Canarypox	(Minke *et al*., 2004)
Recombitek West Nile Virus	West Nile Virus	Horses	prM/E	Canarypox	(Siger *et al*., 2004; Meeusen *et al*., 2007)
PUREVAX Feline Rabies	Rabies	Cats	Glycoprotein	Canarypox	(Meeusen *et al*., 2007)
PUREVAX Recombinant FeLV	Feline leukemia virus	Cats	Env, Gag/pol	Canarypox	(Poulet *et al*., 2003; Meeusen *et al*., 2007)
Recombitek Distemper	Canine distemper Virus	Dogs	HA and F	Canarypox	(Meeusen *et al*., 2007; Stephensen *et al*., 1997)
PUREVAX Ferret Distemper	Canine distemper Virus	Ferrets	HA and F	Canarypox	(Meeusen *et al*., 2007)

Vectormune FP-MG	Mycoplasma Gallisepticum	Poultry	40k and mgc	Fowlpox	(Zhang *et al*., 2010)
Vectormune FP-LT	Laryngo Tracheitis	Poultry		Fowlpox	(Davison *et al*., 2006)
Vectormune FP-ND/	Newcastle disease Virus	Poultry	HN and F	Fowlpox	(Taylor *et al*., 1996; Meeusen e*t al*., 2007)
TROVAC-AIV H5	Avian influenza	Poultry	HA	Fowlpox	(Bublot *et al*., 2006)

Other applications of pox virus based vector

The pox virus vectors can also be looked at as general delivery systems for genes for other applications. For cancer immunotherapy, numerous pox virus-based recombinants expressing tumor-associated antigens or biological response modifiers have been described (Bonnet *et al.,* 2000; Guse *et al.,* 2011). Of particular note, recombinants expressing the carcinoembryonic antigen were shown to elicit both antibody and cellular immune responses in mice and monkeys and to protect mice from tumor cell challenge. Whether vaccinia or canarypox-based recombinants expressing the carcinoembryonic antigen will have any therapeutic benefit is currently being investigated in the clinic in patients with colorectal carcinomas (Flanagan, 2004; Beukema *et al*., 2006; Beukema, 2009). A recent publication reported the protection of mice vaccinated with a p53 expressing recombinant against challenge with an isogenic and highly tumorigenic mouse fibroblast tumor cell line expressing high levels of a mutant human p53 but lacking endogenous murine p53 (Ma *et al*., 2010). Expression of the mutant form of p53 in the recombinant virus was not essential since the wild-type p53 afforded similar efficacy. This may be an important observation since p53 is an attractive target for cancer immunotherapy. Mutations of p53 represent the most common genetic changes demonstrated in human tumors (Vierboom *et al.,* 2000; Blaszczyk-Thurin *et al.,* 2002; Chan *et al.,* 2004).

Currently, highly-attenuated vaccinia strains and avipoxviruses have been extensively assessed in preclinical models, as well as in humans, to determine their immunogenicity and protective efficacy against HIV (Souza *et al.,* 2005; Franchini *et al.,* 2014). Attenuated vaccinia strains and avipoxviruses have been shown to be safe and able to carry HIV genes and express their proteins to induce both antibodies and cellular immune responses (Gómez *et al.,* 2013). Preclinical studies show protection against HIV challenge. When using a live attenuated vector system, one must be cognizant of the potential for immune dampening because of vector-specific immunity. In this regard, avipoxviruses, such as canarypox, appear free of the inhibitory effects of vector immunity and repeated use (Jacobs *et al.,* 2009; Elena *et al.* 2012). In the coming 5 to 10 years, we will certainly know whether this class of vaccine candidates, either alone or in a prime–boost format with other vectors or proteins, willcontribute to HIV disease management either from a preventive or therapeutic perspective (Franchini *et al.,* 2014).

Conclusion and Recommendations

The use of vaccinia virus (VACV) as a smallpox vaccine for nearly two centuries has led to the first deliberate eradication of a human disease from the earth. The use of pox virus-based vectors as heterologous vaccines and the ensuing years of extensive pursuit of this idea have provided numerous working examples in laboratory animal model systems as well as in target species. The work over the last thirty years has raised and resolved many questions related to the safety of poxvirus derived vectors. Vaccinia virus was genetically modified to reduce its pathogenicity and to restrict its broad host range. At the same time, the avipoxviruses were developed as extremely safe and useful recombinant vaccines for birds and mammals.

The recombinant capripoxvirus vaccine containing a cDNA of the peste-des-petits-ruminants virus (PPRV) fusion protein gene was found to protect goats against challenge with a virulent PPRV strain. Poxvirus derived vectors have now been licensed for commercialization and a significant number of clinical studies have been and continue to be pursued for both infectious diseases, ex vivo therapies, and cancer immunotherapy, and they have shown promising trails to prevent serious disease. Given that there are differences between the ability of existing vaccinia virus strains and other poxviruses to function as immunization vehicles, safety and revaccination issues with each vaccine candidate in the target species are raised.

Based on the above conclusion, the following recommendations are forwarded:

- Additional research should be done on the effects of dose and route of immunization, recombinant stability, and sustained heterologous gene expression of pox virus based vector vaccines to enhance safety and immunogenicity.
- VACV-like virus research, host range, transmissibility, and reservoir presence, characterization of unclassified poxviruses, and development of next-generation vaccines could all become much more important.
- Future work concentrating on the rationally designed and careful use of these vectors in the future will allow medics and veterinarians to prevent, cure and eradicate diseases.

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