Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Viral Vectors for Veterinary Vaccines

MICHAEL SHEPPARD

Animal Health Biological Discovery, Pfizer Central Research, Groton, Connecticut 06340

I. Introduction and Background

Numerous reviews have described the use of viral vectors for possible vaccine delivery (e.g., Cavanagh, 1985; Sheppard and Fahey, 1989; Wray and Woodward, 1990; Graham and Prevec, 1992; Boyle and Heine, 1993; Hilleman, 1994; Martin, 1994; Dorner, 1995; Babiuk *et al.*, 1996; Perkus and Paoletti, 1996). However, in this review I will focus solely on the use of viral vectors for delivery of veterinary vaccines. It is without question that vaccination plays an essential role in veterinary medicine, providing the major and often the only prophylatic approach for the control of infectious diseases. In spite of the vast array of currently available vaccines veterinarians and the livestock producers continue to express the need for vaccines that not only maintain the best features of killed or subunit vaccines (such as safety) as well as the best features of conventional modified live vaccines (such as

1093–975X/99 $25.00

efficacy) but improve on them. As well as the need for continual improvement of vaccines there exists a need for new vaccines either to new diseases (e.g., chicken anemia virus or porcine reproductive and respiratory syndrome virus) or to old diseases for which vaccines are not available or no longer meet the requirements of the end user (e.g., bovine virus diarrhea virus vaccines). As well as new vaccines there is also need for vaccines with special features that allow potential customers to design disease control programs that suit their specific needs on top of offering greater safety and improved protection. The design and construction of these new veterinary vaccines is a major challenge facing the field of vaccinology. With the continued demand of improving vaccines and producing new ones it is easier for potential vaccine candidates to fail to meet the increased level of requirements that are expected. The failure of some vaccines can result from problems associated with delivery, such as insufficient or no induction of the appropriate protective immune response. The development of delivery systems to produce vaccines that are more effective, offer greater safety, are convenient to administer, and are compatible with customer practices is part of the challenge for vaccinologists. The development of safe and convenient live viral vectors for the delivery of veterinary vaccines is *one* possible way of meeting some of these challenges. Recombinant DNA technology has allowed more detailed characterization of the genetic organization of many viruses to such an extent that regions suitable for insertion of foreign genetic material have been identified. This has resulted in the development of numerous types of viral vectors from a wide variety of viral families. Some of these viral vectors have been developed with the potential for delivering and expressing gene(s) from a foreign pathogen and so act as a vaccine vector (Table I). The viral vector is often genetically attenuated or cannot complete its replication cycle in the animal to be immunized, and thus produces no clinical disease. Although initially the majority of viral vector development centered around poxviruses, especially vaccinia (Panicali and Paoletti, 1982; Macket *et al.,* 1982), it was not long before viral vector development witnessed a virtual explosion in the types of viruses developed into vectors. These included herpeviruses (Post *et al.,* 1982), adenoviruses (Berkner and Sharp, 1982), retroviruses (Wei *et al.,* 1981), papoviruses (Southern and Berg, 1982), polyoma virus (Fried and Ruley, 1982), picornaviruses (Kitson *et al.,* 1991), Semliki Forest virus (SFV; Zhou *et al.,* 1994), Sindbis virus (Pugachev *et al.,* 1995), and even some plant viruses (Jagadish *et al.,* 1996; Dalsgaard *et al.,* 1997).

TABLE I

CHARACTERISTICS OF THE MORE COMMON VIRUS GROUPS USED AS VECTORS

Characteristics	Pox viruses	Adenoviruses	Herpes viruses	Retroviruses
Genome	180–300 kb	30–45 kb	150–200 kb	9.2 kb
Max. Insert	>30 kb	>5 kb	30 kb	8 kb
Max. Titer	10^7–10^9	10^8–10^{11}	10^6–10^8	10^6–10^9
Administration	Scarification/ injection	Injection/aerosol/ oral	Injection/water	Injection
Safety	Problems with immuno-suppressed	Inflammation	Latency	Genomic insertion
Background expression by vector	Yes	Yes	Yes	No

II. Viral Vector Construction

Greater understanding of the structure and function of a wide range of viruses at the genetic level has opened up ways of designing novel viral vaccine vectors which should improve the quality and effectiveness of some future vaccines as major prophylatic tools. Viral vaccine vectors have really developed from a greater technological understanding of viruses at the genetic level, where today they have become a viable alternative strategy as one method for the delivery of vaccines. The concept of viral vectors was first highlighted by Bernard Moss and others in the early 1980s (Mackett *et al.,* 1982; Panicali and Paoletti, 1982), where they showed that vaccinia virus could be engineered to carry and express foreign genes (Panicali and Paoletti, 1982; Mackett *et al.,* 1982). From the time when Moss and others first demonstrated that vaccinia virus could be developed as a vector for the expression of foreign genes, the technology has been exploited to apply to a variety of virus families as well as a variety of foreign genes including those that encode antigens from pathogens. As a result both DNA and RNA viruses have been developed as viral vaccine vectors (Table I).

To produce viral vaccine vectors it is first necessary to study the genome of the vector to a stage of understanding where at least one region suitable for insertion of foreign genetic material has been iden-

tified. Second, genes from pathogens that encode proteins that will induce an appropriate protective immune response and can be stably integrated into the vector's genome and expressed need to be identified. Finally, it is necessary to insert the foreign gene(s) in such a way as to ensure the correct and sufficient expression of the foreign gene(s).

The ideal viral vaccine vector would have all or at the very least some of the following features:

- Safe and nonpathogenic for the vaccinate
- Evoke the appropriate protective immune response
- Single host or limited host range
- Stable genome
- No integration into the host genome
- Readily accessible region(s) for insertion of foreign genetic material
- Able to tolerate well insertion of foreign genetic material and expression of foreign gene(s)
- Convenient to deliver and fits with management practices
- Relatively simple and cost effective to produce
- Limited background gene expression by the vector

III. Advantages and Disadvantages of Viral Vectors for Vaccine Delivery

Live viral vectors offer several advantages for vaccine delivery compared to killed, subunit, or conventional modified live vaccines. First, because of the possibility of delivering divalent or even perhaps multivalent vaccines, using a single type of vector can result in a single manufacturing process rather than several and possibly even a single vaccination rather than several. Therefore, vectored vaccines have the potential to be less expensive to the manufacturer and the end user. Because the foreign gene is being expressed in the cells of its natural host, it is expected that any post-translational modifications required will be correct and produce an authentic antigen, as opposed to *Escherichia coli* or baculovirus systems (among others) that do not always produce authentic foreign proteins. Depending on the vector selected it may be possible to deliver the vectored vaccine more conveniently to the mammal or bird by spray or water or some other means rather than by needle injection. Such a mass administration approach may be particularly relevant to the poultry industry. The vector could also be constructed to deliver simultaneously an immunomodulator (e.g., gamma interferon), which could modify the type or

magnitude of the immune response to allow the vaccine to be successful or more successful than it would be otherwise. The vector only expresses the antigens from the pathogen that are required to elicit a protective immune response and therefore reduces or eliminates the chance of disease by being exposed to the whole pathogen as with a killed or modified live vaccine. Finally, the appropriate viral vectors will induce both cell-mediated and humoral immune responses and in some cases are particularly suitable for inducing a local immune response in the mucosal surfaces.

One of the main disadvantages of using viral vectors for vaccine delivery is that like subunit vaccines each vector can only deliver one or a relatively small number of foreign antigens to the host animal and therefore rely on those being able to elicit a completely protective immune response. Also the only antigens that can be delivered are those that are encoded by nucleic acid. Thus such things as lipopolysaccharides are not deliverable. With any vector, regardless of type, only a limited amount of foreign genetic material can be inserted into the vector's genome stably and expressed appropriately. One must always be wary of altered tissue tropisms due to the expression of the foreign gene(s). Of course the effectiveness of a viral vector is limited by preexisting immune response in the animal from prior exposure to the virus used to construct the vector. Finally, as with all live vaccines there is the problem of shelf life and compatibility with other vaccine preparations.

IV. Construction of Safer Viral Vectors for Vaccine Delivery

To produce viral vaccine vectors successfully it is necessary to ensure that the vector itself does not pose any disease threat to the animal that receives the vaccination or to the person delivering the vaccine to the animal. Most often this is achieved by attenuating the viral vector in some way. Until recent times the means of generating a live attenuated virus had been entirely empirical. This process usually involved the passaging of the virus in cell culture or animals that were not the natural host, followed by testing of the resulting viruses for decreased virulence in the natural host. The basis for attenuation is most often unknown, and may be a result from as minor as a single base change, and thus the chance of reversion back to virulence is always a possibility. This type of traditional method for generating a live attenuated virus is not necessarily the most attractive method for generating a viral vaccine vector. With the advent of molecular biology and our

improved knowledge of viruses at the genetic level it is now possible to generate live attenuated viruses with precise genetic changes, improving their safety and thus make them more suitable as vectors for vaccine delivery.

A. Deletion of Nonessential Genes

A good example is the deletion of the thymidine kinase (TK) gene. While the deletion of the TK gene has little or no effect on virus growth in cell culture, TK deleted viruses can be significantly attenuated *in vivo* ((Buller *et al.,* 1985; Kit *et al.,* 1985, 1986; Becker *et al.,* 1986). This feature has been exploited successfully for the development of live attenuated herpesvirus vaccines (McGregor *et al.*, 1985; Kit *et al.,* 1985; Marchioli *et al.,* 1987; Moorman *et al.,* 1990) as well as safer herpesvirus and poxvirus vectors (e.g., Buller *et al.*, 1985; Bayliss *et al.,* 1991; Mulder *et al.,* 1994; Hu *et al.,* 1997).

B. Deletion of Essential Genes

If an essenential gene is deleted from a virus, the virus can only grow if the gene or gene product is provided in trans. This virus is phenotypically normal but genotypically defective and cannot replicate in the host because the deleted gene product is not available. This type of virus can replicate *in vitro* with the help of a genetically engineered supporting cell line that expresses the deleted gene product. The stage of the virus life cycle of which the gene product is required will govern how far through the replication cycle a virus will proceed. In some cases (e.g., if the essential deleted gene is required for virus penetration of the cell) the virus will complete a single round of replication in the host but the progeny viruses will not be able to invade any other cell. (Farrell *et al.,* 1994; McLean *et al.,* 1994; Peeters *et al.,* 1994). However, if the deleted essential gene is an early gene that is required to activate other viral genes, then the number of viral proteins synthesized may be limited and the viral genome may not be able to complete even a single cycle of replication (Chen and Knipe, 1996; Brehm *et al.,* 1997; Da Costa *et al.,* 1997).

C. Replication Limited Virus

A third alternative, which has been exploited successfully, is to use a virus that can only completely replicate in one species as a vector in another species, where it cannot complete an entire cycle of replication but can commence a replication cycle sufficiently to allow expression of

the foreign gene (Tartaglia *et al.,* 1992). The canarypox virus (CPV) vector, termed *ALVAC,* has successfully been exploited to the degree of commercial success. The CPV is restricted to avian cells only for productive replication but can be used to vaccinate mammals where it can elicit an immune response to the foreign gene product without completing an entire cycle of replication (Tartaglia *et al.,* 1992, 1993; Taylor *et al.,* 1995). The human adenovirus type 5 (HAV-5) has also been exploited in a similar fashion to the CPV (Table III) but has the disadvantage that this virus is a human pathogen and so has yet to be exploited commercially.

Several other strategies are also available and in some cases have been exploited successfully in order to generate safe viral vectors for vaccine delivery. Table V (next section) provides a summary of some of these possible approaches.

V. Examples of Reported Viral Veterinary Vaccine Vectors

Even though there are a great many examples of viral vectors reported in the literature since they were first described in 1982, the number of publications reporting the use of viral vectors for veterinary vaccine delivery is not that large. After searching for published papers that describe viral vectors with veterinary vaccine applications, especially those that could be described as purposely developed for veterinary use, the obvious conclusion was that even though this research was first described in 1982 the veterinary side is still in its infancy. Publications describing viral vectors for veterinary vaccine delivery can be divided into several groups, which are represented in the following tables: Table II, poxvirus vectors; Table III, adenovirus vectors; Table IV, herpesvirus vectors; and Table V, other virus vectors. Although these four tables probably do not include every single publication describing viral vectors for veterinary vaccine delivery they do describe the majority of published papers and present the reader with an idea of the limited amount of research that has occurred in this field during the last 15 years.

VI. Commercially Available Viral Vaccine Vectors for Veterinary Use

At the time of writing this review only three viral vectored vaccines for use in the veterinary field have been licensed for release. All three are based on poxvirus vectors and the three vectors represent the

TABLE II

POXVIRUS VECTORS FOR THE DELIVERY OF VETERINARY VACCINES

Vector	Pathogen	Antigen	Test animal	Reference
CPV	RHDV	Capsid	Rabbit	Fischer *et al.*, (1997)
RPV	FPV/rabies	VP2/G	Cat	Hu *et al.*, (1997)
CPV/VV	CDV	F/HA	Ferret	Stephensen *et al.*, (1997)
FPV	NDV	F/HN	Chicken	Taylor *et al.*, (1996)
Myxoma	Influenza	HA	Rabbit	Kerr and Jackson (1995)
SPV	PrV	gp50/gp63	Swine	van der Leek *et al.*, (1994)
CPV	FeLV	env/gag	Cat	Tartaglia *et al.*, (1993)
VV	Rabies	G	Fox	Brochier *et al.*, (1991)
PPV	NDV	F	Chicken	Latellier *et al.*, (1991)
FPV	NDV	HA/NA	Chicken	Boursnell *et al.*, (1990a)
FPV	NDV	HN/F	Chicken	Boursnell *et al.*, (1990b)
VV	BLV	env	Rabbit	Ohishi *et al.*, (1990)
VV	EHV-1	gp13	Mouse	Guo *et al.*, (1989)
VV	PrV	gp50/63/I/X	Mouse	Kost *et al.*, (1989)
FPV	Rabies	G	Dog/cat	Taylor *et al.*, (1988)
VV	FeLV	env	Cat	Gilbert *et al.*, (1987)
VV	Rabies	G	Fox	Blancou *et al.*, (1986)
VV	Rabies	G	Mouse	Kieny *et al.*, (1984)

Key: VV, vaccinia virus; FPV, fowl poxvirus; PPV, pigeon poxvirus; SPV swine poxvirus; CPV, canary poxvirus; RHDV, rabbit hemorrhagic disease virus; CDV, canine distemper virus; FPV, feline parvovirus; PrV, pseudorabies virus; FeLV, feline leukemia virus; NDV, Newcastle disease virus; BLV, bovine leukosis virus; EHV, equine herpes virus.

TABLE III

ADENOVIRUS VECTORS FOR THE DELIVERY OF VETERINARY VACCINES

Vector	Pathogen	Antigen	Test animal	Reference
OAV	*Tinea ovis*	45W	Sheep	Rothel *et al.*, (1997)
HAV-5	PRCV	Spike	Swine	Callebaut *et al.*, (1996)
HAV-5	TGE	Spike	Swine	Torres Iet al., (1996)
HAV-5	Rabies	G	Skunk	Yarosh *et al.*, (1996)
HAV-5	BCV	HEG	Cotton rat	Bacca-Estrada *et al.*, (1995)
HAV-5	FIV	env	Cat	Gonin *et al.*, (1995)
HAV-5	PRCV	Spike	Swine	Callebaut *et al.*, (1994)
HAV-5	PrV	gD	Swine	Adam *et al.*, (1994)
HAV-5	Rabies	G	Dog	Prevec *et al.*, (1990)
HAV-5	PrV	gp50	Rabbit/mouse	Eloit *et al.*, (1990)

Key: OAV, ovine adenovirus; HAV-5, human adenovirus type 5; PRCV, porcine respiratory corona virus; TGE, transmissible gastroenteritis virus; BCV, bovine corona virus; PrV, pseudorabies virus.

TABLE IV

HERPES VIRUS VECTORS FOR THE DELIVERY OF VETERINARY VACCINES

Vector	Pathogen	Antigen	Test animal	Reference
HVT	NDV	HN/F	Chicken	Reddy *et al.*, (1996)
HVT	MDV	gpAB	Chicken	Reddy *et al.*, (1996)
FHV-1	FeLV	env	Cat	Willemse *et al.*, (1996)
PrV	HCV	gpE1	Swine	Mulder *et al.*, (1994)
HVT	MDV	gpB	Chicken	Ross *et al.*, (1993)
BHV-1	PrV	gpC	Swine	Kit *et al.*, (1992)
FHV-1	FeLV	gag/env	Cat	Wardley *et al.*, (1992)
BHV-1	FMDV	cp-epitopes	Cattle	M. Kit *et al.*, (1991)
BHV-1	FMDV	cp-epitopes	Cattle	S. Kit *et al.*, (1991)
PrV	HCV	gpE1	Swine	van Zijl *et al.*, (1991)

Key: HTV, herpes virus of turkeys; FHV, feline herpes virus; BHV, bovine herpes virus; PrV, pseudorabies virus; NDV, Newcastle disease virus; MDV, Marek's disease virus; FMDV, foot-and-mouth disease virus; HCV, hog cholera virus.

evolution in poxvirus vector development. The first vector approved was the vaccinia virus vector carrying the rabies G glycoprotein gene (e.g., Kieny *et al.*, 1984; Blancou *et al.*, 1986; Brochier *et al.*, 1991). In terms of complying with the characteristics of a desirable vector for vaccine delivery in the veterinary setting, this vector has the greatest number of undesirable characteristics. However, it satisfied an unmet need and as a result was released in various parts of the world. The second vector to be licensed for release was the fowlpox virus vector. This vector delivers the Newcastle disease virus HN and F genes and is designed to vaccinate poultry (e.g., Boursnell *et al.*, 1990a,b; Taylor *et al.*, 1996). While this vector has the desirable characteristic of only replicating in poultry it also has some limitations that affect its use in the field. The third vector licensed is the canarypox virus vector and represents the state-of-the-art poxvirus vector. This vector was developed to deliver the HA and F genes of canine distemper virus and is the most recently available of the three vector vaccines (e.g., Stephensen *et al.*, 1997).

VII. Summary

Whatever strategy is adopted for the development of viral vectors for delivery of veterinary vaccines there are several key points to consider: (1) Will the vectored vaccine give a delivery advantage compared to

TABLE V

OTHER VIRUS VECTORS FOR THE DELIVERY OF VETERINARY VACCINES

Vector	Pathogen	Antigen	Test animal	Reference
CPMV	MEV	VP2 epitope	Mink	Dalsgaard *et al.* (1997)
Poliovirus	FMDV	Epitopes	Guinea pig	Kitson *et al.* (1991)
Retrovirus	NDV	HN	Chicken	Morrison *et al.* (1990)
Retrovirus	Influenza	HA	Chicken	Hunt *et al.* (1988)

OTHER ALTERNATIVE VIRAL VECTORS THAT HAVE THE POTENTIAL FOR VETERINARY VACCINE DELIVERY

Amplicons	VLPs	SFV	Sinbis	Bacteriophage
Frenkel *et al.* (1994)	Jagadish *et al.* (1996)	Atkins *et al.* (1996)	Pugachev *et al.* (1995)	Bastien *et al.* (1997)
Smith *et al.* (1995)	Porter *et al.* (1996)	Mossman *et al.* (1996)		
Fink *et al.* (1996)	Roy (1996)	Zhou *et al.* (1995)		
Pechan *et al.* (1996)	Schodel *et al.* (1994a)	Zhou *et al.* (1994)		
Starr *et al.* (1996)	Schodel *et al.* (1994b)			

Key: CPMV, cowpea mosaic virus; MEV, mink enteritis virus.

what's already available? (2) Will the vectored vaccine give a manufacturing advantage compared to what's already available? (3) Will the vectored vaccine provide improved safety compared to what's already available? (5) Will the vectored vaccine increase the duration of immunity compared to what's already available? (6) Will the vectored vaccine be more convenient to store compared to what's already available? (7) Is the vectored vaccine compatible with other vaccines? If there is no other alternative available then the answer to these questions is easy. However, if there are alternative vaccines available then the answers to these questions become very important because the answers will determine whether a vectored vaccine is merely a good laboratory idea or a successful vaccine.

REFERENCES

Adam, M., Lepottier, M. F., and Eloit, M. (1994). Vaccination of pigs with replication-defective adenovirus vectored vaccines: The example of pseudorabies. *Vet. Microbiol.* **42,** 205–215.

Atkins, G. J., Sheahan, B. J., and Liljestrom, P. (1996). Manipulation of the Semliki Forest virus genome and its potential for vaccine construction. *Mol. Biotechnol.* **5,** 33–38.

Babiuk, L. A., van Drunen Littel-van den Hurk, S., Tikoo, S. K., Lewis, P. J., and Liang, X. (1996). Novel viral vaccines for livestock. *Vet. Immunol. Immunopathol.* **54,** 355–363.

Bacca-Estrada, M. E., Liang, X., Babiuk, L. A., and Yoo, D. (1995). Induction of mucosal immunity in cotton rats to haemagglutinin-esterase glycoprotein of bovine coronavirus by recombinant adenovirus. *Immunology* **86,** 134–140.

Bastien, N., Trudel, M., and Simard, C. (1997). Protective immune responses induced by the immunization of mice with a recombinant bacteriophage displaying an epitope of the human respiratory syncytial virus. *Virology* **234,** 118–122.

Bayliss, C. D., Peters, R. W., Cook, J. K. A., Reece, R. L., Howes, K., Binns, M. M., and Boursnell, M. E. G. (1991). A recombinant fowlpox virus that expresses the VP2 antigen of infectious bursal disease virus induces protection against mortality caused in the virus. *Arch. Virol.* **120,** 193–205.

Becker, Y., Hadar, J., Taylor, E., Ben-Hur, T., Raibstein, I., Rosen, A., and Darai, G. (1986). A sequence in HpaI P fragment of herpes simplex virus 1 DNA determines intraperitoneal virulence in mice. *Virology* **149,** 255–259.

Berkner, K. L., and Sharp, P. A. (1982). Preparation of adenovirus recombinants using plasmids of viral DNA. *In* "Eukaryotic Viral Vectors" (Y. Gluzman, ed.), pp. 193–198. Cold Spring Harbor Lab., Cold Spring Harbor, NY.

Blancou, J., Kieny, M. P., Lathe, R., Lecocq, J. P., Pastoret, P. P., Soulebot, J. P., and Desmettre, P. (1986). Oral vaccination of the fox against rabies using a live recombinant vaccinia virus. *Nature* **322,** 373–375.

Boursnell, M. E. G., Green, P. F., Campbell, J. I. A., Deuter, A., Peters, R. W., Tomley, F. M., Samson, A. C. R., Emmerson, P. T., and Binns, M. M. (1990a). A fowlpox virus vaccine vector within insertion sites in the terminal repeats: Demonstration of the efficacy using the fusion gene of Newcastle disease virus. *Vet. Microbiol.* **23,** 305–316.

Boursnell, M. E. G., Green, P. F., Samson, A. C. R., Campbell, J. I. A. Deuter, A., Peters, R. W., Millar, N. S., Emmerson, P. T., and Binns, M. M. (1990b). A recombinant fowlpox virus expressing the hemagglutinin-neuraminidase gene of Newcastle disease virus (NDV). Protects chickens against by NDV. *Virology* **178,** 297–300.

Boyle, D. B., and Heine, H. G. (1993). Recombinant fowlpox virus vaccines for poultry. *Immunol. Cell Biol.* **71,** 391–397.

Brehm, M. A., Bonneau, R. N., Knipe, D. M., and Tevethia, S. S. (1997). Immunization with a replication-deficient mutant of herpes simplex virus type 1 (HSV-1) induces a CD8+ cytotoxic T-lymphocyte response and confers a level of protection comparable to that of wild-type HSV-1. *J. Virol.* **71,** 3534–3544.

Brochier, B., Kieny, M. P., Costy, F., Coppens, P., Bauduin, B., Lecocq, J. P., Languet, B., Chappuis, G., Desmettre, P., Afiademanyo, K., Libois, R., and Pastoret, P. P. (1991). Large-scale eradication of rabies using recombinant vaccinia-rabies vaccine. *Nature* **354,** 520–522.

Buller, R. M. L., Smith, G. L., Cremer, K., Notkins, A., and Moss, B. (1985). Decreased virulence of recombinant vaccinia virus expressed vectors is associated with a thymidine kinase negative phenotype. *Nature* **317,** 813–815.

Callebaut, P., Pensaert, M., and Enjuanes, L. (1994). Construction of a recombinant adenovirus for the expression of the glycoprotein S antigen of porcine respiratory coronavirus. *In* "Coronaviruses" (H. Lande and J. F. Vantherot, eds.), pp. 469–470. Plenum, New York.

Callebaut, P., Enjuanes, L., and Pensaert, M. (1996). An adenovirus recombinant expressing the spike glycoprotein of porcine respiratory coronavirus is immunogenic in swine. *J. Gen. Virol.* **77,** 309–313.

Cavanagh, D. (1985). Viral and bacterial vectors of immunogens. *Vaccine* **3,** 45–48.

Chen, Y. M., and Knipe, D. M. (1996). A dominant mutant form of the herpes simplex virus ICP8 protein decreases viral late gene transcription. *Virology* **221,** 281–290.

Da Costa, X. J., Bourne, N., Stanberry, L. R., and Knipe, D. M. (1997). Construction and characterization of a replication-defective herpes simplex virus 2 ICP8 mutant strain and its use in immunization studies in a guinea pig model of genital disease. *Virology* **232,** 1–12.

Dalsgaard, K., Uttenthal, A., Jones, T. D., Xu, F., Merryweather, A., Hamilton, W. D. O., Langeveld, J. P. M., Boshuizen, R. S., Kamstrup, S., Lomonossoff, G. P., Porta, C., Vela, C., Casal, J. I., Meloen, R. H., and Rodgers, P. B. (1997). Plant-delivered vaccine protects target animals against a viral disease. *Nat. Biotechnol.* **15,** 248–252.

Dorner, F. (1995). An overview of vaccine vectors. *Dev. Biol. Stand.* **84,** 23–32.

Eloit, M., Gilardi- Hebenstreit, P., Toma, B., and Perricaudet, M. (1990). Construction of a defective adenovirus vector expressing the pseudorabies virus glycoprotein gp50 and its use as a live vaccine. *J. Gen. Virol.* **71,** 2425–2431.

Farrell, H. E., McClean, C. S., Harley, C., Efstathiou, S., Inglis, S., and Minson, A. C. (1994). Vaccine potential of a herpes simplex virus type 1 mutant with an essential gene deleted. *J. Virol.* **68,** 927–932.

Fink, D. J., DeLuca, N. A., Goins, W. F., and Glorioso, J. C. (1990). Gene transfer to neurons using herpes simplex virus based vectors. *Annu. Rev. Neurosci.* **19,** 265–287.

Fischer, L., LeGros, F.-X., Mason, P. W., and Paoletti, E. (1997). A recombinant canarypox virus protects rabbits against a lethal rabbit hemorrhagic disease virus (RHDV) challenge. *Vaccine* **15,** 90–96.

Frenkel, N., Singer, O., and Kwong, A. D. (1994). Minireview: The herpes simplex virus amplicon—a versatile defective virus vector. *Gene Ther.* **1,** Suppl. 1, S40–S46.

Fried, M., and Ruley, E. (1982). Use of polyoma virus vector. *In* "Eukaryotic Viral Vectors" (Y. Gluzmann, ed.), pp. 67–70. Cold Spring Harbor Lab., Cold Spring Harbor, NY.

Gilbert, J. H., Pedersen, N. C., and Nunberg, J. H. (1987). Feline leukemia virus envelope protein expression encoded by a recombinant vaccinia virus: Apparent lack of immunogenicity in vaccinated animals. *Virus Res.* **7,** 49–67.

Gonin, P., Fournier, A., Oualikene, W., Moraillon, A., and Eloit, M. (1995). Immunization trial of cats with a replication defective adenovirus type 5 expressing the ENV gene of feline immunodeficiency virus. *Vet. Microbiol.* **45,** 393–401.

Graham, F. L., and Prevec, L. (1992). Adenovirus-based expression vectors and recombinant vaccines. *In* "Vaccines: New Approaches to Immunological Problems" (R. W. Ellis, ed.), pp. 363–430. Butterworth-Heinemann, Boston.

Guo, P. X., Goebel, S., Davis, S., Perkus, M. E., Languet, B., Desmettre, P., Allen, G., and Paoletti, E. (1989). Expression in recombinant vaccinia virus of the equine herpesvirus 1 gene encoding glycoprotein 13 and protection of immunized animals. *J. Virol.* **63,** 4189–4198.

Hilleman, M. R. (1994). Recombinant vector vaccines in vaccinology. *Dev. Biol. Stand.* **82,** 3–20.

Hu, L., Ngichabe, C., Trimarchi, C. V., Esposito, J. J., and Scott, F. W. (1997). Raccoon poxvirus live recombinant feline panleukopenia virus VP2 and rabies virus glycoprotein bivalent vaccine. *Vaccine* **15,** 1466–1472.

Hunt, L. A., Brown, D. W., Robinson, H. L., Naeve, C. W., and Webster, R. G. (1988). Retrovirus-expressed hemagglutinin protects against lethal influenza virus infections. *J. Virol.* **62,** 3014–3019.

Jagadish, M. N., Edwards, S. J., Hayden, M. B., Grusovin, J., Vandenberg, K., Schoofs, P., Hamilton, R. C., Shukla, D. D., Kalnins, H., McNarmara, M., Haynes, J., Nisbet, I. T., Ward, C. W., and Pye, D. (1996). Chimeric potyvirus-like particles as vaccine carriers. *Intervirology* **39,** 85–92.

Kerr, P. J., and Jackson, R. J. (1995). Myxoma virus as a vaccine vector for rabbits—antibody levels to influenza virus hemagglutinin presented by a recombinant myxoma virus. *Vaccine* **13,** 1722–1726.

Kieny, M. P., Lathe, R., Drillen, R., Spehner, D., Skory, S., Schmitt, D., Wiktor, T., Koprowski, H., and Lecocq, J. P. (1984). Expression of rabies virus glycoprotein from a recombinant vaccinia virus. *Nature* **312,** 163–166.

Kit, M., Kit, S., Little, S. P., DiMarchi, R. D., and Gale, C. (1991). Bovine herpesvirus-1 (infectious bovine rhinotracheitis virus)-based viral vectors which expresses foot-and-mouth disease epitopes. *Vaccine* **9,** 564–572.

Kit, S., Kit, M., and Pirtle, E. C. (1985). Attenuated properties of thymidine kinase-negative deletion mutant of pseudorabies virus. *Am. J. Vet. Res.* **46,** 1359–1367.

Kit, S., Kit, M., and McConnell, S. (1986). Intramuscular and intravaginal vaccination of pregnant cows with thymidine kinase-negative, temperature-resistant infectious bovine rhinotracheitis virus (bovine herpesvirus 1). *Vaccine* **4,** 55–61.

Kit, S., Kit, M., DiMarchi, R. D., Little, S. P., and Gale, C. (1991). Modified-live infectious bovine rhinotracheitis virus vaccine expressing monomer and dimer forms of foot-and-mouth disease cupsid protein epitopes on surface of hybrid virus particles. *Arch. Virol.* **120,** 1–17.

Kit, S., Otsuka, H., and Kit, M. (1992). Expression of porcine pseudorabies virus genes by a bovine herpesvirus-1 (infectious bovine rhinotracheitis virus) vector. *Arch. Virol.* **124,** 1–20.

Kitson, J. D. A., Burke, K. L., Pullen, L. A., Belsham, G., and Almond, J. W. (1991). Chimeric polioviruses that include sequences derived from two independent antigenic sites of foot-and-mouth disease virus (FMDV) induce neutralizing antibodies against FMDV in guinea pigs. *J. Virol.* **65,** 3068–3075.

Kost, T. A., Jones, E. V., Smith, K. M., Reed, A. P., Brown, A. L., and Miller, T. J. (1989). Biological evaluation of glycoproteins mapping to two distinct mRNAs within the BamHI fragment 7 of pseudorabies virusi expression of the coding regions by vaccinia virus. *Virology* **171,** 365–376.

Letellier, C., Burny, A., and Meulemans, G. (1991). Construction of a pigeonpox virus recombinant: expression of the Newcastle disease virus (NDV) fusion glycoprotein and protection of chickens against NDV challenge. *Arch. Virol.* **118,** 43–56.

Mackett, M., Smith, G. L., and Moss, B. (1982). Vaccinia virus: A selectable eukaryotic cloning and expression vector. *Proc. Natl. Acad. Sci. USA* **79,** 7415–7419.

Marchioli, C. C., Yancey, R. J., Wardley, R. C., Thomsen, D. R., and Post, L. E. (1987). A vaccine strain of pseudorabies virus with deletions in the thymidine kinase and glycoprotein X genes. *Am. J. Vet. Res.* **48,** 1577–1583.

Martin, S. J. (1994). Vaccine design: Future possibilities and potentials. *Biotechnol. Adv.* **12,** 619–624.

McGregor, S., Easterday, B. C., Kaplan, A. S., and Ben-Porat, T. (1985). Vaccination of swine with thymidine kinase-deficient mutants of pseudorabies virus. *Am. J. Vet. Res.* **46,** 1494–1497.

McLean, C. S., Erturk, M., Jennings, R., Ni Challanain, D., Minson, A. C., Duncan, I., Boursnell, M. E. G., and Inglis, S. C. (1994). Protective vaccination against primary and recurrent disease caused by herpes simplex virus (HSV) type 2 using a genetically disabled HSV-1. *J. Infect. Dis.* **170,** 1100–1109.

Moorman, R. J. M., deRover, T., Briaire, J., Peters, B. P. H., Gielkens, A. L. J., and van Oirschot, J. T. (1990). Inactivation of the thymidine kinase gene of a gI deletion mutant of pseudorabies virus generates a safe but still highly immunogenic vaccine strain. *J. Gen. Virol.* **71,** 1591.

Morrison, T., Hinshaw, V. S., Sheerer, M., Cooley, A. J., Brown, D., McQuain, C., and McGinnes, L. (1990). Retroviral expressed hemagglutinin-neuraminidase protein protects chickens from Newcastle disease virus induced disease. *Microbiol. Pathol.* **9,** 387–396.

Mossman, S. P., Bex, F., Berglund, P., Arthos, J., O'Neil, S. P., Riley, D., Maul, D. H., Bruck, C., Momin, P., Burny, A., Fultz, P. N., Mullins, J. I., Liljestrom, P., and Hoover, E. A. (1996). Protection against lethal simian immunodeficiency virus SIVsmmPBj14 disease by a recombinant Semliki Forest virus gp160 vaccine and by a gp120 subunit vaccine. *J. Virol.* **70,** 1953–1960.

Mulder, W. A. M., Priem, J., Glazenburg, K. L., Wagenaar, F., Gruys, E., Gielkens, A. L. J., Pol, J. M. A., and Kimman, T. G. (1994). Virulence and pathogenesis of non-virulent and virulent strains of pseudorabies virus expressing envelope glycoprotein E1 of hog cholera virus. *J. Gen. Virol.* **75,** 117–124.

Ohishi, K., Suzuki, H., Maruyama, T., Yamamoto, T., Funahashi, S., Miki, K., Ikawa, Y., and Sugimoto, M. (1990). Induction of neutralizing antibodies against bovine leukosis virus in rabbits by vaccination with recombinant vaccinia virus expressing bovine leukosis virus envelope glycoprotein. *Am. J. Vet. Res.* **51,** 1170–1173.

Panicali, D., and Paoletti, E. (1982). Construction of poxviruses as cloning vectors: Insertion of the thymidine kinase gene from herpes simplex virus into the DNA of infectious vaccinia virus. *Proc. Natl. Acad. Sci. USA* **79,** 4927–4931.

Pechan, P. A., Fotaki, M., Thompson, R. L., Dunn, R., Chase, M., Chiocca, E. A., and Breakefield, X. O. (1996). A novel 'piggyback' packaging system for herpes simplex virus amplicon vectors. *Hum. Gene Ther.* **7,** 2003–2013.

Peeters, B., Bouma, A., deBruin, T., Moorman, R., Gielkens, A., and Kimman, T. (1994). Non-transmissible pseudorabies virus gp50 mutants: A new generation of safe live vaccines. *Vaccine* **12,** 375–380.

Perkus, M. E., and Paoletti, E. (1996). Recombinant virus as vaccination carrier of heterologous antigens. *In* "Concepts in Vaccine Development" (S. H. E. Kaufman, ed.), pp. 379–422. de Gruyter, Berlin.

Porter, D. C., Melsen, L. R., Compans, R. W., and Morrow, C. D. (1996). Release of virus-like particles from cells infected with poliovirus replicons which express human immunodeficiency virus type 1 Gag. *J. Virol.* **70,** 2643–2649.

Post, L. E., Norrild, B., Simpson, T., and Roizman, B. (1982). Chicken ovalbumin gene fused to a herpes simplex virus a promoter and linked to a thymidine kinase gene is regulated like a viral gene. *Mol. Cell. Biol.* **2,** 233–240.

Prevec, L., Campbell, J. B., Christie, B. S., Belbeck, L., and Graham, F. L. (1990). A recombinant human adenovirus vaccine against rabies. *J. Infect. Dis.* **161,** 27–30.

Pugachev, K. V., Mason, P. W., Shope, R. E., and Frey, T. K. (1995). Double-subgenomic sindbis virus recombinants expressing immunogenic proteins of Japanese encephalitis virus induce significant protection in mice against lethal JEV infection. *Virology,* **212,** 587–594.

Reddy, S. K., Sharma, J. M., Ahmad, J., Reddy, D. N., McMillen, J. K., Cook, S. M., Wild, M. A., and Schwartz, R. D. (1996). Protective efficacy at a recombinant herpesvirus of turkeys as an *in ovo* vaccine against Newcastle and Marek's disease in specific-pathogen-free chickens. *Vaccine* **14,** 469–477.

Ross, L. J., Binns, M. M., Typers, P., Pastorek, J., Zelnik, V., and Scott, S. (1993). Construction and properties of a turkey herpesvirus recombinant expressing the Marek's disease virus homologue of glycoprotein B of herpes simplex virus. *J. Gen. Virol.* **74,** 371–377.

Rothel, J. S., Boyle, D. B., Both, G. W., Pye, A. D., Waterkeyn, J. G., Wood, P. R., and Lightowlers, M. W. (1997). Sequential nucleic acid and recombinant adenovirus vaccination induces host-protective immune responses against *Taenia ovis* infection in sheep. *Parasite Immunol.* **19,** 221–227.

Roy, P. (1996). Genetically engineered particulate virus-like structures and their use as vaccine delivery systems. *Intervirology* **39,** 62–71.

Schodel, F., Peterson, D., Hughes, J., and Milich, D. (1994a). Hepatitis B virus core particles as a vaccine carrier moiety. *Int. Rev. Immunol.* **11,** 153–165.

Schodel, F., Wirtz, R., Peterson, D., Hughes, J., Warren, R., Sudoff, J., and Milich, D. (1994b). Immunity to malaria elicited by hybrid hepatitis B virus core particles carrying circumsporozoite protein epitopes. *J. Exp. Med.* **180,** 1037–1046.

Sheppard, M., and Fahey, K. J. (1989). Herpesviruses and adenoviruses as potential vectors for the poultry industry. *Aust. Vet. J.* **66,** 421–423.

Smith, R. L., Geller, A. I., Escudero, K. W., and Wilcox, C. L. (1995). Long-term expression in sensory neurons in tissue culture from herpes simplex virus type 1 (HSV-1) promoters in an HSV-1-derived vector. *J. Virol.* **69,** 4593–4599.

Southern, P., and Berg, P. (1982). Mammalian cell transformation with SV40 vector. *In* "Eukaryotic Viral Vectors" (Y. Gluzman, ed.), pp. 41–45. Cold Spring Harbor Lab., Cold Spring Harbor, NY.

Starr, P. A., Lim, F., Grant, F. D., Trask, L., Lang, P., Yu, L., and Geller, A. I. (1996). Long-

term persistence of defective HSV-1 vectors in the rat brain is demonstrated by reactivation of vector gene expression. *Gene Ther.* **3,** 615–623.

Stephensen, C. B., Welter, J., Thaker, S. R., Taylor, J., Tartaglia, J., and Paoletti, E. (1997). Canine distemper virus (CDV) infection of ferrets as a model for testing Morbillivirus vaccine strategies: NYVAC- and ALVAC-based CDV recombinants protect against symptomatic infection. *J. Virol.* **71,** 1506–1513.

Tartaglia, J., Perkus, M. E., Taylor, J., Norton, E. K., Audonnet, J.-C., Cox, W. I., Davis, S. W., VanderHoeven, J., Meignier, B., Riviere, M., Languet, B., and Paoletti, E. (1992). NYVACP: A highly attenuated strain of vaccinia virus. *Virology* **188,** 217–232.

Tartaglia, J., Jarrett, O., Neil, J. C., Desmettre, P., and Paoletti, E. (1993). Protection of cats against feline leukemia virus by vaccination with a canarypox virus recombinant, ALVAC-FL. *J. Virol.* **67,** 2370–2375.

Taylor, J., Weinberg, R., Languet, B., Desmettre, P., and Paoletti, E. (1988). Recombinant fowlpox virus inducing protective immunity in non-avian species. *Vaccine* **6,** 497–503.

Taylor, J., Meignier, B., Tartaglia, J., Languet, B., VanderHoeven, J., Franchini, G., Trimarchi, C., and Paoletti, E. (1995). Biological and immunogenic properties of a canarypox-rabies recombinant, ALVAC-RG (vCP65) in non-avian species. *Vaccine* **13,** 539–549.

Taylor, J., Christensen, L., Gettig, R., Goebel, J., Bouquet, J. F., Mickle, T. R., and Paoletti, E. (1996). Efficacy of a recombinant fowlpox-based Newcastle disease virus vaccine candidate against velogenic and respiratory challenge. *Avian Dis.* **40,** 173–180.

Torres, J. M., Alonso, C., Ortega, A., Mittal, S., Graham, F., and Enjuanes, L. (1996). Tropism of human adenovirus type 5-based vectors in swine and their ability to protect against transmissible gastroenteritis coronavirus. *J. Virol.* **70,** 3770–3780.

van der Leek, M. L., Feller, J. A., Sorensen, G., Isaacson, W., Adams, C. L., Borde, D. J., Pfeiffer, N., Tran, T., Moyer, R. W., and Gibbs, E. P. (1994). Evaluation of swinepox virus as a vaccine vector in pigs using Aujeszky's disease (pseudorabies) virus gene insert coding for glycoproteins gp50 and gp63. *Vet. Rec.* **134,** 13–18.

van Zijl, M., Wensvoort, G., deKluyver, E., Hulst, M., van der Gulden, H., Gielkens, A., Berns, A., and Moormann, R. (1991). Live attenuated pseudorabies virus expressing envelope glycoprotein E1 of hog cholera virus protects swine against both pseudorabies and hog cholera. *J. Virol.* **65,** 2761–2765.

Wardley, R. C., Berlinski, P. J., Thomsen, D. R., Meyer, A. L., and Post, L. E. (1992). The use of feline herpesvirus and baculovirus as vaccine vectors for the gag and env genes of feline leukemia virus. *J. Gen. Virol.* **73,** 1811–1818.

Wei, C.-M., Gibson, M., Spear, P. G., and Scolnick, E. M. (1981). Construction and isolation of a transmissible retrovirus containing the src gene of Harvey murine sarcoma virus and the thymidine kinase gene of herpes simplex virus type 1. *J. Virol.* **39,** 935–944.

Willemse, M. J., van Schooneveld, S. H. B., Chalmers, W. S. K., and Sondermeijer, P. J. A. (1996). Vaccination against feline leukemia using a new feline herpesvirus type I vector. *Vaccine* **14,** 1511–1516.

Wray, C., and Woodward, M. S. (1990). Biotechnology and veterinary science: Production of veterinary vaccines. *Rev. Sci. Tech. Off. Int. Epizoot.* **9,** 779–794.

Yarosh, O. K., Wandeler, A. I., Graham, F. L., Campbell, J. B., and Prevec, L. (1996). Human adenovirus type 5 vectors expressing rabies glycoprotein. *Vaccine* **14,** 1257–1264.

Zhou, X., Berglund, P., Rhodes, G., Parker, S. E., Jondal, M., and Liljestrom, P. (1994).

Self replicating Semliki Forest virus RNA as recombinant vaccine. *Vaccine* **12,** 1510–1514.

Zhou, X., Berglund, P. Zhao, H., Lilijestrom, P., and Jondal, M. (1995). Generation of cytotoxic and humoral immune responses by nonreplicative recombinant Semliki Forest virus. *Proc. Natl. Acad. Sci. USA* **92,** 3009–3013.