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# Endogenous retroviruses as potential hazards for vaccines

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ABSTRACT

Retroviruses are classified as exogenous or endogenous according to their mode of transmission. Generally, endogenous retroviruses (ERVs) are not pathogenic in their original hosts; however, some ERVs induce diseases. In humans, a novel gammaretrovirus was discovered in patients with prostate cancer or chronic fatigue syndrome. This virus was closely related to xenotropic murine leukemia virus (X-MLV) and designated as xenotropic murine leukemia virus-related virus (XMRV). The origin and transmission route of XMRV are still unknown at present; however, XMRV may be derived from ERVs of rodents because X-MLVs are ERVs of inbred and wild mice. Many live attenuated vaccines for animals are manufactured by using cell lines from animals, which are known to produce infectious ERVs; however, the risks of infection by ERVs from xenospecies through vaccination have been ignored. This brief review gives an overview of ERVs in cats, the potential risks of ERV infection by vaccination, the biological characteristics of RD-114 virus (a feline ERV), which possibly contaminates vaccines for companion animals, and the methods for detection of infectious RD-114 virus.



## 1. Exogenous and endogenous retroviruses (ERVs)

Retroviruses are classified as exogenous or endogenous according to their mode of transmission. Exogenous retroviruses are transmitted horizontally by infection, and they infect somatic cells but not germ line cells. On the other hand, endogenous retroviruses (ERVs) are retroviruses that have been integrated into germ line cells [5]. ERVs are inherited by offspring from parents in a classical Mendelian fashion. ERVs occupy about 10% of mammalian genomes and are mostly inactivated by deletions and mutations with stop codons [5]; however, some ERVs retain open reading frames (ORFs) which encode proteins. Certain ERVs express envelope proteins (Env) that block pathogenic exogenous retroviruses; for instance, cats express the Env of endogenous feline leukemia virus (FeLV) that block exogenous FeLV subgroup B [10].

Exogenous retroviruses are classified into seven genera, *i.e.*, alpharetrovirus, betaretrovirus, gammaretrovirus, deltaretrovirus, epsilonretrovirus, spumaretrovirus, and lentivirus. ERVs are divided into at least three classes, I, II and III [5]. Type I ERV is closely related to exogenous counterparts of gammaretrovirus and epsilonretrovirus. Type II and III ERVs are similar to alpharetrovirus and betaretrovirus, and spumavirus, respectively.

## 2. Potential risk of infection by ERVs

Technical innovation of animal engineering enables us to develop genetically engineered pigs for the purpose of xenotransplanting pig organs or tissues to humans; however, pigs have replication-competent ERVs, termed porcine ERVs (PERVs) [17]. The discovery of PERVs able to infect human cells led to the halt of the clinical trials of xenotransplantation, and the risks of PERVs in xenotransplantation have been investigated extensively. Due to the presence of infectious ERVs in non-human species, the control subjects in xenotransplantation were expanded by the recent definition of xenotransplantation. Xenotransplantation (from animals to humans) is now defined as follows; any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues or organs from a non-human animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live non-human cells, tissues or organs.

Generally, ERVs are not pathogenic in their original hosts; however, some ERVs induce diseases; for example, ERVs from AKR mice induce lymphoma in their hosts [11]. Certain ERVs infect new hosts and induce diseases; there was an incident in which an ERV from Asian rodents infected Gibbon apes and induced lymphoma [19]. Moreover, a retrovirus emerged in koalas in Australia about two hundred years ago, and endogenized [19]. The virus, named koala retrovirus, induces neoplastic diseases and immune suppression in the new host. In humans, a novel gammaretrovirus was discovered recently in patients

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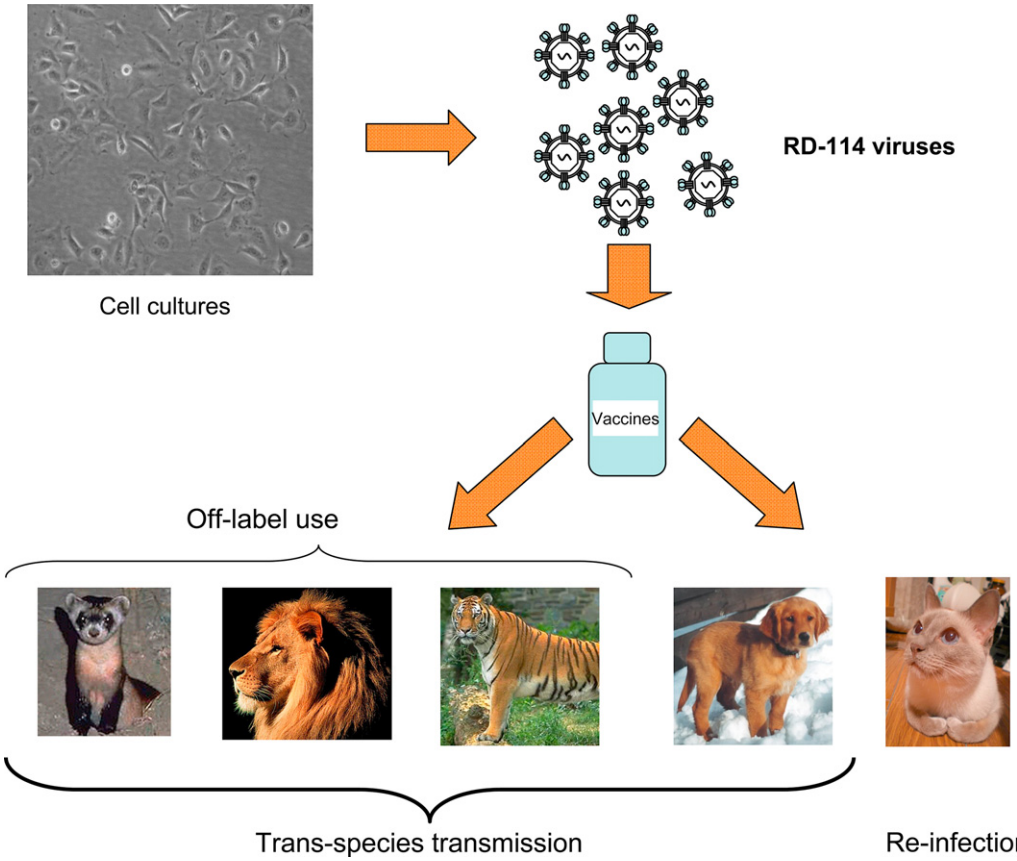


**Fig. 1.** Potential risks of contamination of RD-114 virus in live attenuated vaccines. Certain feline cell lines produce RD-114 viruses. If these cells are used for manufacturing vaccines for feline and canine infectious viral agents, RD-114 virus will contaminate the vaccines. RD-114 virus-contaminated vaccines may be used in companion animals and exotic animals as off-label use.

with prostate cancer [21]. This virus was closely related genetically to the xenotropic murine leukemia virus (X-MLV) and designated as xenotropic murine leukemia virus-related virus (XMRV). Currently, it is still controversial whether XMRV induces prostate cancer; however, several reports have been published, strengthening the link between infection with XMRV and prostate cancer in the USA. Quite recently, XMRV was found to be frequently isolated from patients with chronic fatigue syndrome in the USA [8] and a relationship between XMRV infection and the disease is suspected. The origin and transmission route of XMRV are still unknown at present; however, XMRV is considered to be derived from ERVs of rodents because X-MLVs are ERVs of inbred and wild mice.

In the veterinary science area, at least mice, pigs, cats and chickens have infectious ERVs. Many live attenuated vaccines for animals are manufactured by using cell lines from these animals. In addition, several live attenuated vaccines are manufactured by using cells which are known to produce infectious ERVs; however, the risks of infection by ERVs from xenospecies have been ignored. According to the definition, the use of vaccines manufactured using cells from xenospecies is not xenotransplantation. The discovery of XMRV prompted us to study the risks of ERVs in live attenuated vaccines. This brief review focuses on feline ERVs possibly contaminating vaccines for companion animals.

## 3. ERVs in cats

At least two ERVs, endogenous FeLV and RD-114 virus, are present in the cat genome. In addition to these ERVs, two additional ERVs have been reported. Bonner and Todaro reported that cats may contain a third group of ERV, distantly related to the primate virus MAC-1 [2]. Haapala et al. also reported a novel endogenous retrovirus which is related to RD-114 virus [6]; however, no further studies have been performed on these ERVs. There are about 20 copies of endogenous FeLV in the cat genome, and at least two loci have ORF encoding Env [7]. Extensive genetic analyses revealed that there is no infectious locus in the cat genome. On the other hand, all domestic cats (*Felis catus*) have an entire RD-114 genome and sometimes the virus is produced spontaneously or induced in vitro from feline cells by several chemical reagents [14].

## 4. Biological characteristics of RD-114 virus

Besides domestic cats, the provirus of RD-114 virus is also present in the genome of other feline species belonging to the genus *Felis*; however, there is no information on whether they also have infectious loci. RD-114 viral genomes have not been detected in large felids, such as lions and pumas; therefore, it is considered that RD-114 virus endogenized in the ancestral species of the genus *Felis* before branching into each species of the genus. In early studies, RD-114 virus was found to be closely related to baboon endogenous retrovirus (BaEV); therefore, RD-114 virus was considered to have originated in baboons. Van der Kyel et al. reported that RD-114 virus is a recombinant virus between a feline endogenous retrovirus termed FcEV and a type D simian retrovirus [22]. The *gag–pol* region of RD-114 virus is similar to gammaretroviruses, and the *env* region is closely related to betaretroviruses and is nearly identical to BaEV. Now, it is considered that BaEV infected an ancestor of the domestic cat lineage, but it was a *de novo* recombinant that made its way into the cat germ line [22].