Primate lentivirus

Molecular phylogenetic studies coupled to virus–host specificity indicated that lentiviruses probably originated in non-primate mammals, and that they can be split into two major classes: primate non-primate lentiviruses. Of the lentiviruses HIV-2 and SIV offer several unique benefits as the basis for lentiviral vector design.

- HIV-1, HIV-2 and SIV remain the only known primate lentiviruses, and consequently are among the most extensively studied viruses known.
- pathogenicity and rates of transmission of HIV-2 and SIV fall far below that of HIV-1,
- HIV-2 and SIV are viruses which may be studied within non-human primate models susceptible to AIDS-like disease* making vectors based upon these viruses accessible to substantial preclinical evaluation.

*models for HIV-1 infection do not develop AIDS-like disease

HIV2 and SIV

HIV-2 and SIV are similar; HIV-2 (a human virus) displaying greater sequence homology with SIV than HIV-1

Sequence relatedness:

- between HIV-2 and SIV is approximately 75%,
- HIV-2 and SIV display less than 50% homology to HIV-1

Nomenclature for the SIV subtypes is based upon the primate species from which prototypic viral strains representative of the subtype was isolated.
Five distinct lentiviruses have been obtained from non-human primates native to Africa:
Chimpanzees (SIVCPZ),
Sooty mangabees (SIVSM),
African green monkeys (SIVAGM),
Mandrills (SIVMND),
Sykes (SIVSYK).
Rhesus macaques (SIVMAC)
Nemestrina macaques (SIVMNE)
Stump-tailed macaques (SIVSTM)
possibly acquired

HIV-2 and FIV infection

Cellular receptor

Initial infection is mediated by binding of the viral surface glycoprotein gp120 to a cellular **CD4** molecule which serves as the primary receptor for all of the primate lentiviruses.
the chemokine receptors **CCR5 and CXCR4** were identified as the principal lentiviral co-receptors.

HIV-2 and SIV Vector Systems

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James R. Gilbert and Flossie Wong-Staal

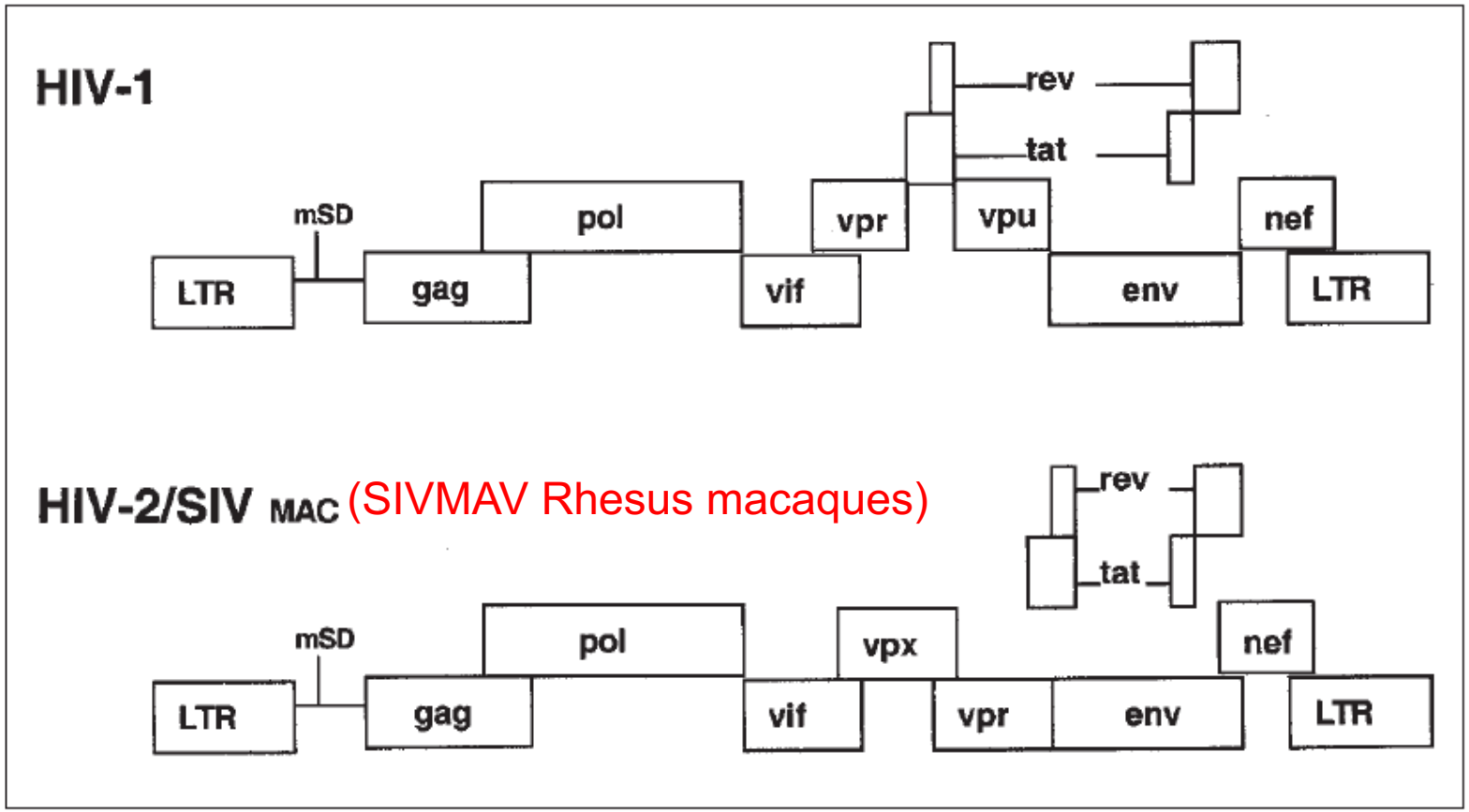
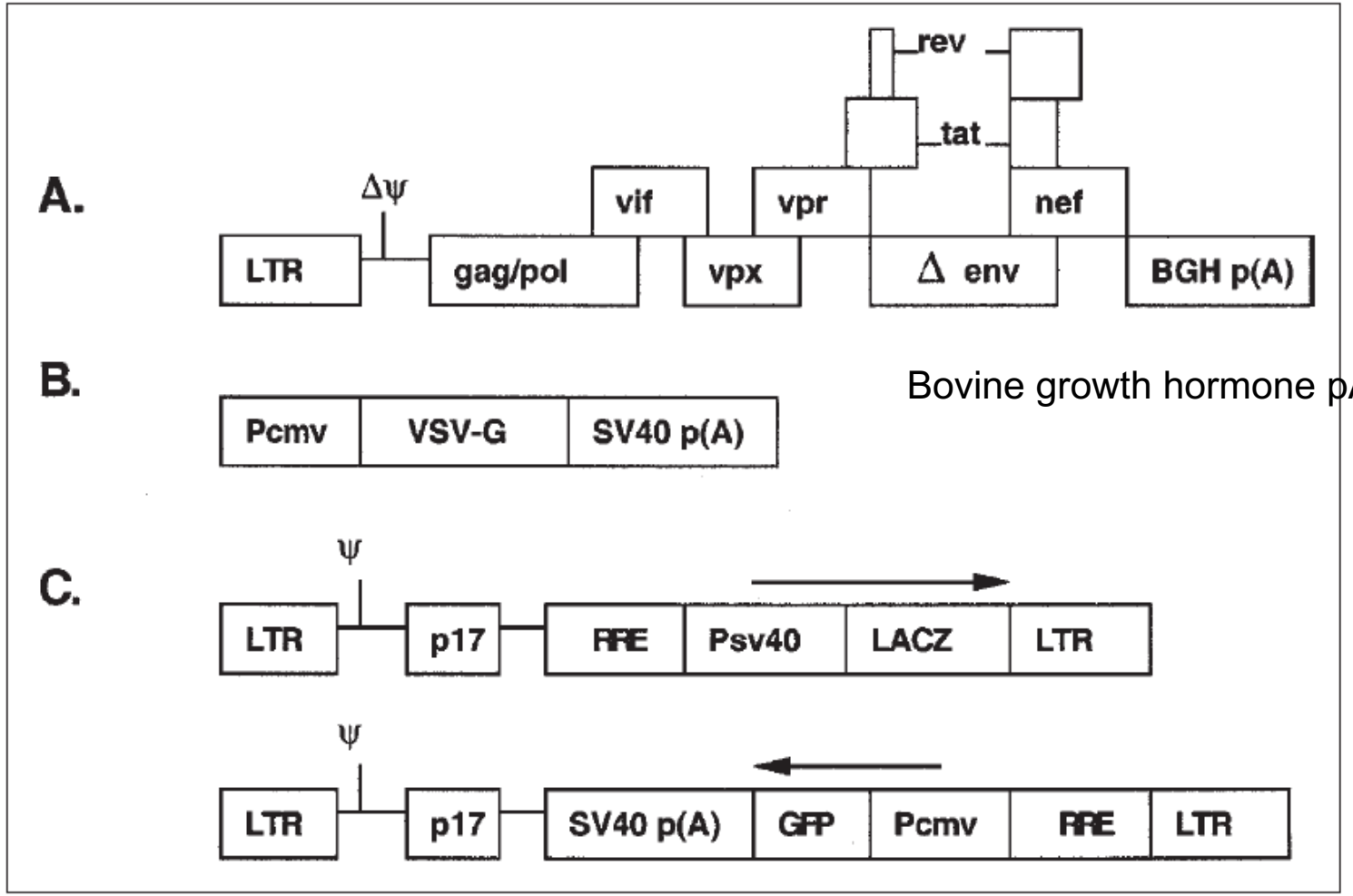


Fig. 1 Genomic organization of HIV-1 and HIV-2/SIV_{MAC}. The relative locations of the structural, regulatory, and accessory genes are indicated, MSD, major splice donor.

Gilbert 2002

Other lentiviral vectors

HIV-2



Bovine growth hormone pA

Fig. 2. A. Design of the HIV-2 packaging construct described in the text. Deletions within the packaging signal and *env* are indicated. The bovine growth hormone polyadenylation signal is positioned precisely at the translational termination codon of *nef*, replacing the 3' LTR. B. The VSV-G expression plasmid, pCMV-G. The *lacZ* and GFP transfer vectors described in the text. GFP is expressed in an antisense orientation relative to LTR expression, whereas *lacZ* expression is in a sense orientation.

Gilbert 2001

non-primate lentiviruses

Molecular phylogenetic studies coupled to virus–host specificity indicated that lentiviruses probably originated in non-primate mammals, and that they can be split into two major classes: primate non-primate lentiviruses.

Non-Primate Lentivirus	Natural Host
visna-maedi virus (VMV)	Sheep
caprine arthritis encephalitis virus (CAEV)	Goat
equine infectious anaemia virus (EIAV)	Horse
feline immunodeficiency virus (FIV)	Cat
bovine immunodeficiency virus (BIV)	Cattle
Jembrana disease virus (JDV)	Bali cattle

Table 2. Differential distribution of accessory genes among non-primate lentivirus genomes.

Accessory Gene	Non-Primate Lentivirus					
	VMV	CAEV	EIAV	FIV	BIV	JDV
rev	+	+	+	+ [a]	+	+
vif	+	+	-	+	+	+
tat	+ [b]	+ [b]	+	-	+	+
orfS	+	+	+	+ [c]	-	-
vpy/vpw	-	-	-	-	+	-
tmx	-	-	-	-	+	+
s2	-	-	+	-	-	-

[a] The Rev protein of FIV bears a divergent non-consensus nuclear export signal; [b] Tat proteins from VMV and CAEV lack the transactivation function; [c] *orfS* gene of FIV is called *orf2*.

Rev (nuclear export of viral genomic RNA), is conserved

Tat, acts as a strong transactivator by binding a stem-loop recognition element in the long terminal repeat (LTR)

Similar morphology:

- spherical-shaped particles of approximately 100 nm;
- core, viral genome is packaged by the nucleocapsid proteins and bound to the reverse transcriptase, integrase, and protease viral enzymes;
- capsid, the core is then encased in a proteinaceous shell and in turn surrounded by matrix protein;
- Envelope, surface appears rough due to the presence of the viral envelope transmembrane and surface glycoproteins.

Similar genome organization:

- a diploid genome of two single-stranded positive-sense RNA molecules;
- three primary *gag*, *pol*, and *env* genes;
- two long-terminal repeats;
- A small set of accessory genes, differentiall distributed among non-primate lentivirus species.

non-primate lentiviruses

FIV Vector Systems

Sybille L. Sauter[1] and Mehdi Gasmi[2]

- Isolato da Davis (Pedersen et al, 1987, Science) dai linfociti del sangue periferico del gatto domestico.
- Infezioni da FIV sono diffuse in tutto il mondo tra tutti i felini, gatti domestici inclusi.
- Non è patogeno per l'uomo
- Il genoma è semplice e trattabile come HIV-1

Comparison of lentivirus genomes

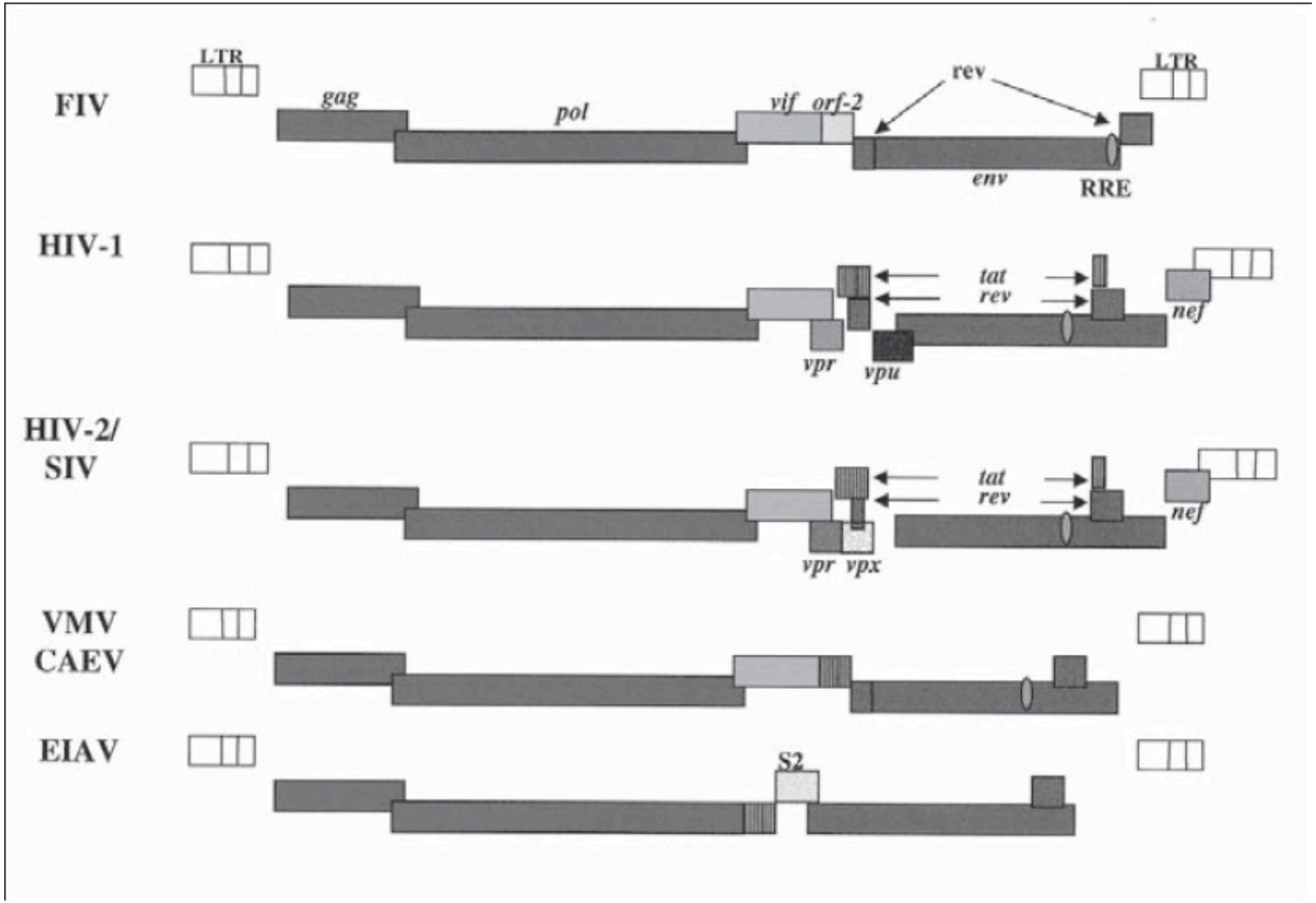
Feline immunodeficiency virus

Human immunodeficiency virus 1

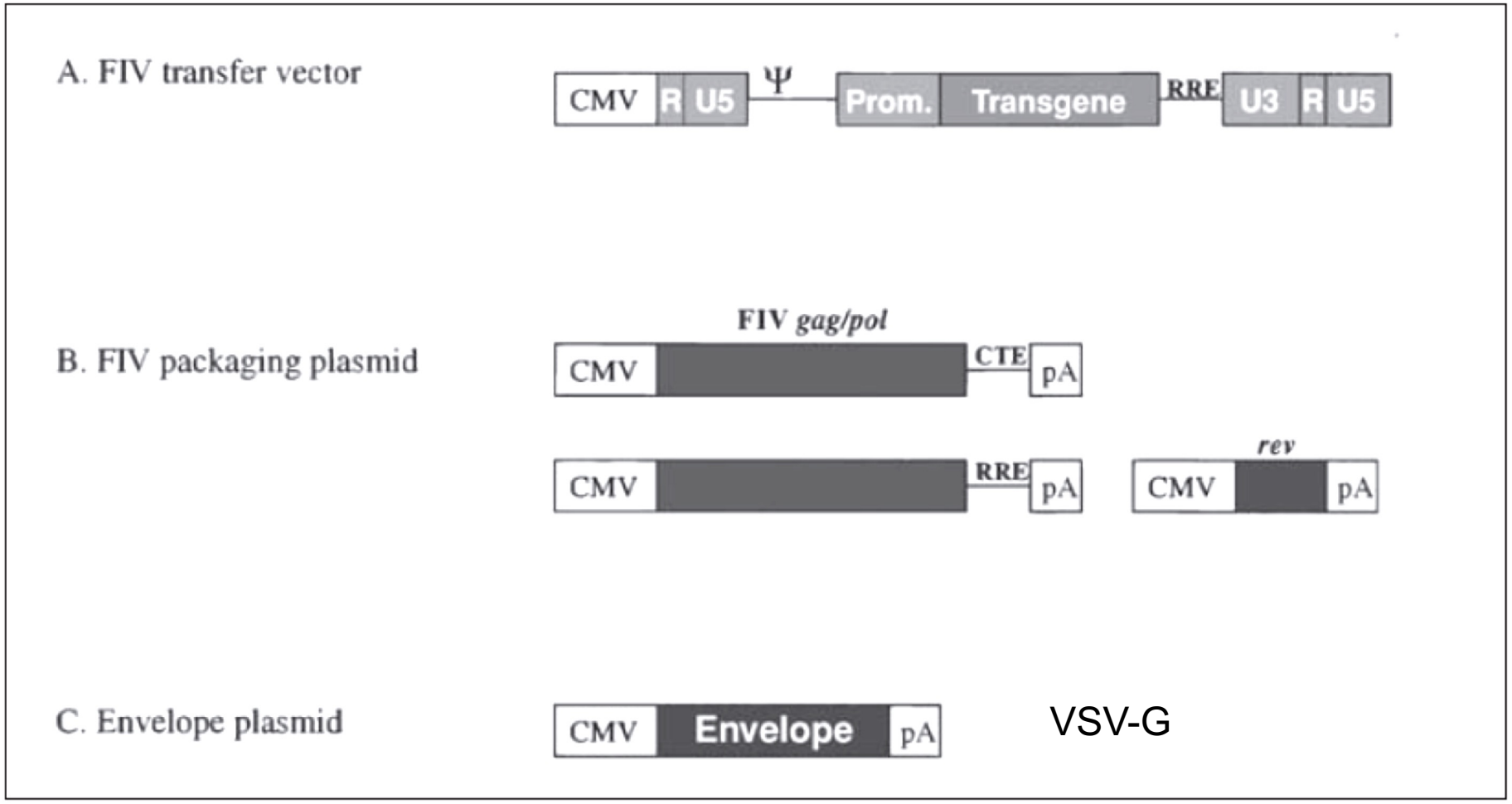
Human immunodeficiency virus 2
Simian immunodeficiendy virus

Visna-medi virus
Caprine arthritis encephalitis virus

Equine infectious anemia virus



FIV vector system



In vivo transduction by VSV-G pseudotyped FIV-vector

Hamster muscle cells /Murine cerebellum (Purkinje cells)/ Rabbit airway epithelium

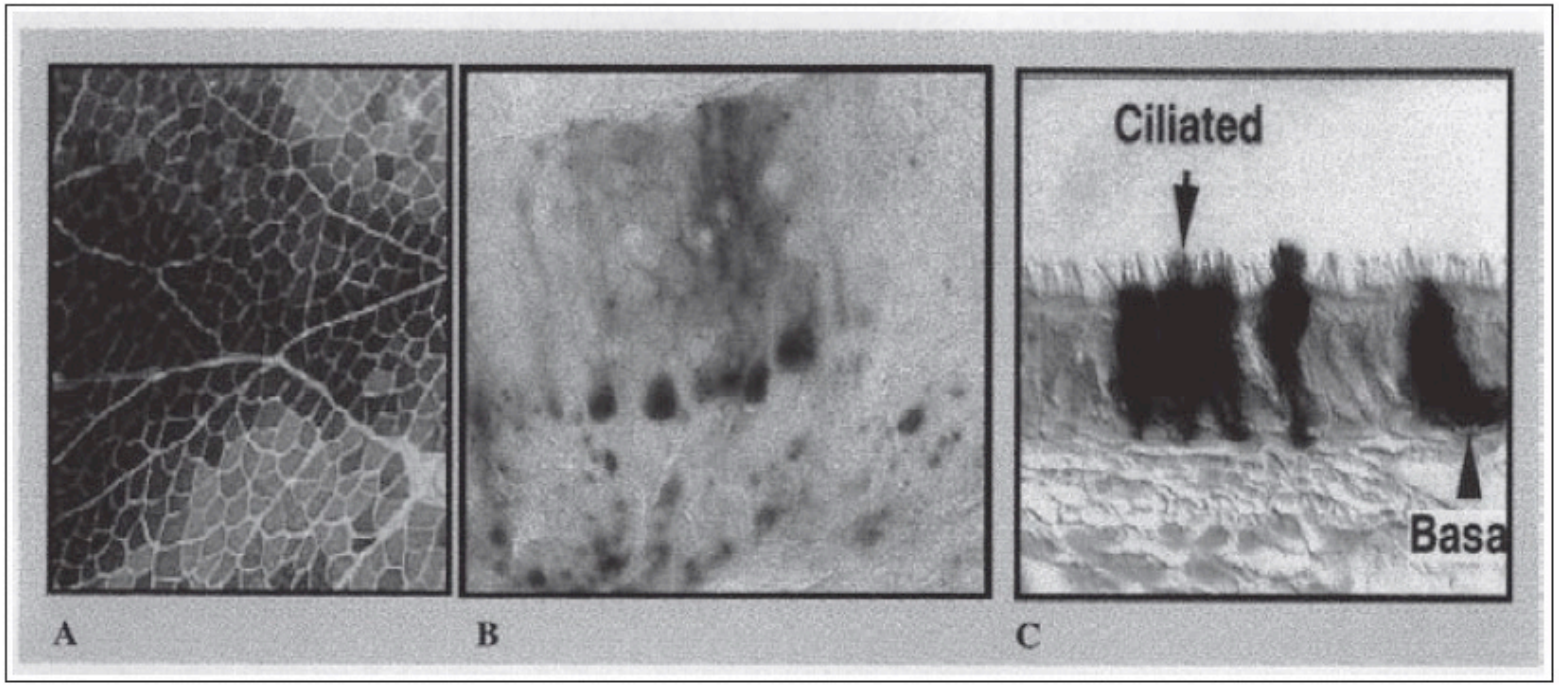


Fig. 4. In vivo transduction by a VSV-G pseudotyped FIV vector of (A) hamster muscle;[158] (B) Purkinje cells in the murine cerebellar lobule ($2x10^5$ cfu, day 21), courtesy of Dr. Beverly Davidson; and (C) rabbit airway epithelium transduced from the apical side.[214] Various cell types of the airway epithelium including ciliated and basal cells are transduced (indicated by arrows).

non-primate lentiviral vectors for ocular gene delivery.

the eye is an excellent target for gene therapy applications:
it is easily accessed by standard injection of therapeutic lentiviral vectors,
it is isolated from the rest of the body via the blood–retina barrier .
These minimize dissemination from the target ocular structures, lowering the risk of side effects (insertional mutagenesis, in non-target cell types

The first lentiviral vector evaluated was derived from the primate HIV lentivirus.
Toxicity, biodistribution, and shedding characteristics of FIV-, BIV- and EIAV-derived vectors have been examined intra-ocularly by several studies.

Table 3. Overview of studies using non-primate lentiviral vectors for ocular gene delivery.

Non-Primate Lentiviral Vector	Target Host Cell/Tissue/Organism	Delivered Genes	References
FIV	Perfused human eyes	*lacZ, eGFP*	[95,96]
FIV	Macaque	*lacZ*	[97]
FIV	Mouse	*lacZ, β-glucuronidase*	[98]
BIV	Mouse	*eGFP*	[99]
EIAV	Rabbit and human corneas, murine corneal endothelial cells	*lacZ, eGFP*	[100]
FIV	Rabbit, rat	*lacZ*	[101]
EIAV	Mouse	*eGFP*	[102]
EIAV	Mouse	*lacZ*	[103]
EIAV	Cryopreserved primary cultured human corneal endothelial cells	*eGFP*	[104]
FIV	Mouse retinal progenitor cells	*YFP*	[105]
FIV	Cat	*eGFP/myocilin* [a], *lacZ*	[106]
EIAV	Mouse	*lacZ, human ABCA4*	[107]
EIAV	Mouse	*endostatin/angiostatin* [a]	[108]
FIV	Macaque	*eGFP*	[109]
FIV	Rabbit	*NBCe1-shRNA/copepod-GFP* [a]	[110]
EIAV (RetinoStat)	Rabbit, macaque	*endostatin/angiostatin* [a]	[111]
EIAV (StarGen)	Rabbit, macaque	*ABCA4*	[112]
EIAV (EncorStat)	Rabbit, primate and human corneal tissue	*endostatin/angiostatin* [a]	[113,114]
EIAV (UshStat)	Mouse, macaque	*myo7A*	[115]
EIAV (RetinoStat)	Human patients	*endostatin/angiostatin* [a]	[116]

[a] the indicated transcription units were co-delivered from lentiviral vectors bearing bicistronic transgenes.

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viruses

MDPI

Review

Non-Primate Lentiviral Vectors and Their Applications in Gene Therapy for Ocular Disorders

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