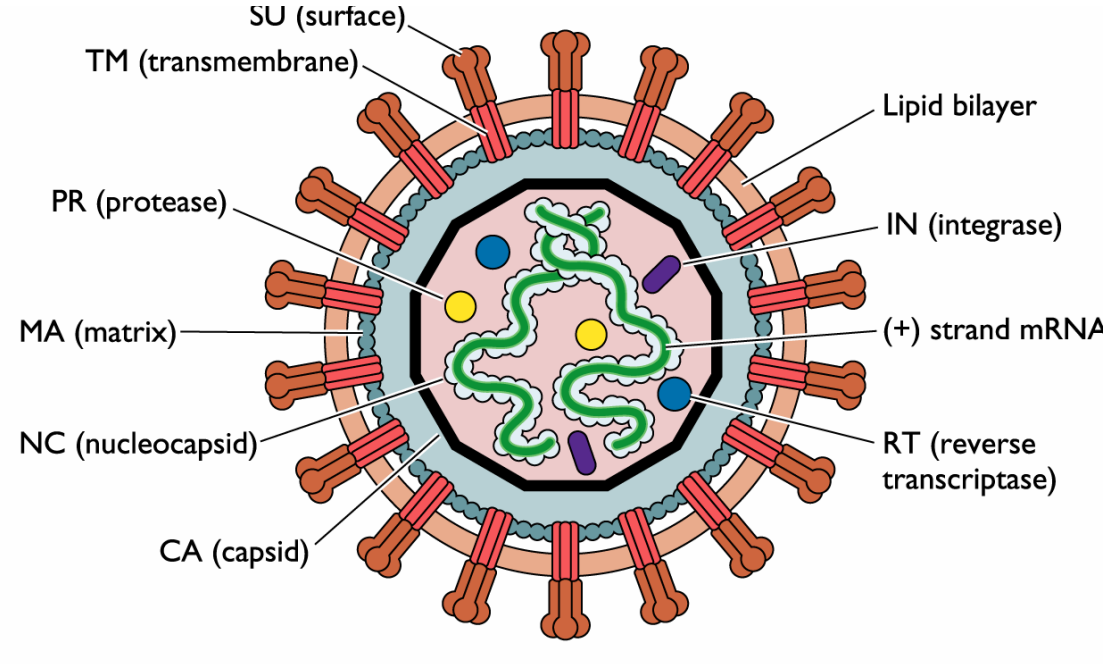
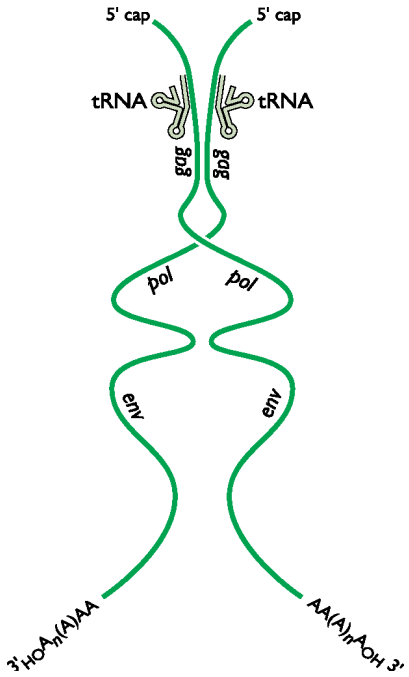
TABLE 47.1 Retrovirus Genera

Name	Examples	Morphology
Alpharetrovirus	Avian leukosis virus (ALV) Rous sarcoma virus	C type
Betaretrovirus	Mouse mammary tumor virus (MMTV) Mason-Pfizer monkey virus (M-PMV) Jaagsiekte sheep retrovirus	B, D type
Gammaretrovirus	Murine leukemia viruses (MuLV) Feline leukemia virus (FeLV) Gibbon ape leukemia virus (GaLV) Reticuloendotheliosis virus (RevT)	C type
Deltaretrovirus	Human T-lymphotropic virus type 1, 2 Bovine leukemia virus (BLV) Simian T-lymphotropic virus type 1, 2, 3	Rod-shaped core
Epsilonretrovirus	Walleye dermal sarcoma virus Walleye epidermal hyperplasia virus 1	–
Lentivirus	Human immunodeficiency virus type 1 Human immunodeficiency virus type 2 Simian immunodeficiency virus (SIV) Equine infectious anemia virus (EIAV) Feline immunodeficiency virus (FIV) Caprine arthritis encephalitis virus (CAEV) Visna/maedi virus	Rod/Cone-shaped cores
Spumavirus	Human foamy virus	Immature

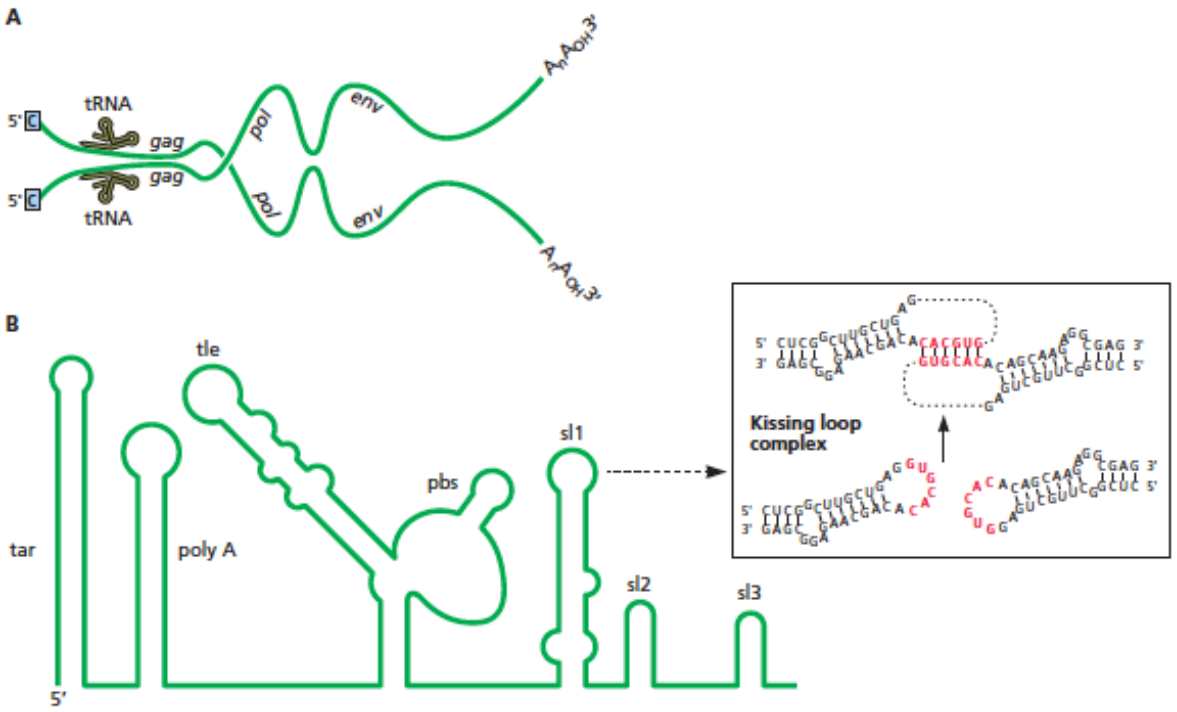
Retroviridae





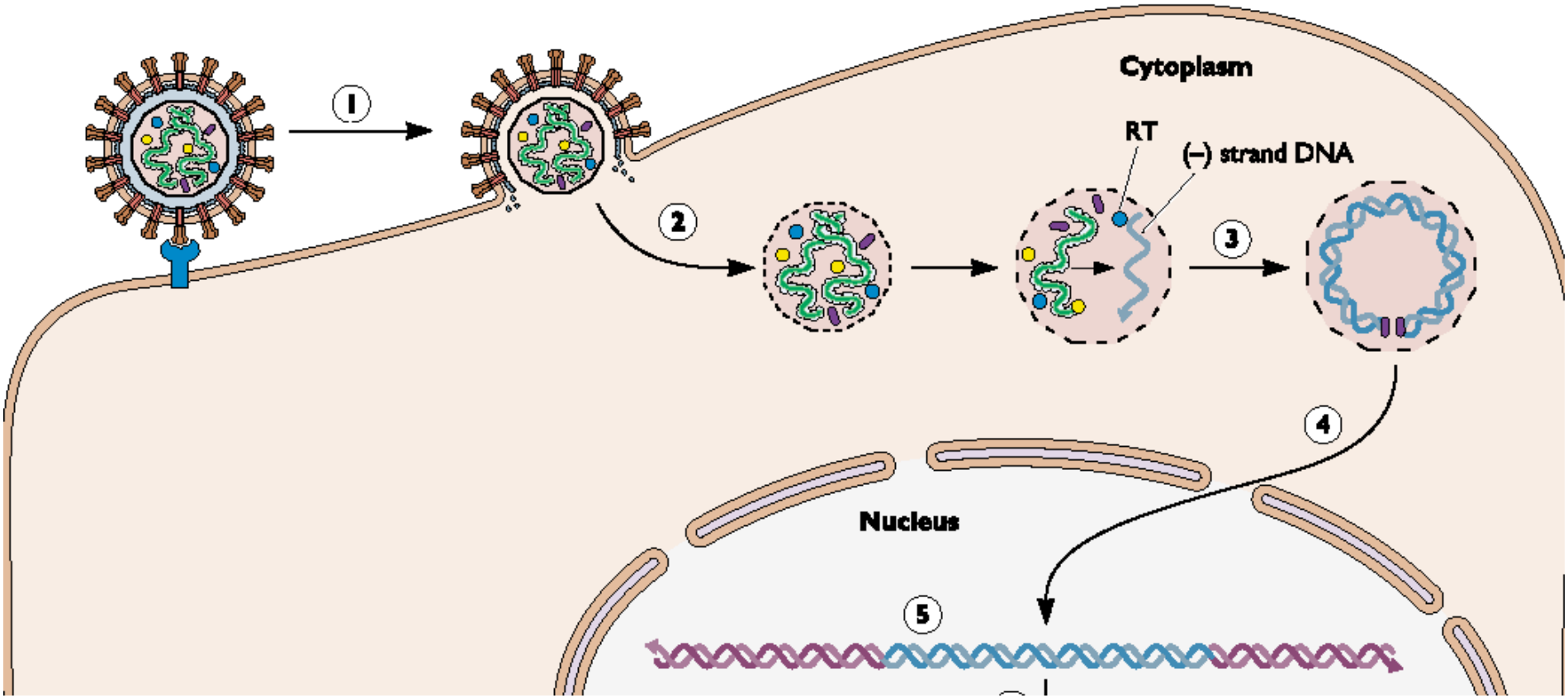
From Flint et al. *Principles of Virology* (2000), ASM Press

The diploid retroviral genome and a dimerization domain



(A) The diploid retroviral genome. Points of contact represent multiple short regions of complementary base pairing. (B) Structural elements in the 5’ end of genomic RNA comprise distinct stem-loop structures. In the human immunodeficiency virus RNA, these elements include the Tat-binding site (tar), a poly(A) stem-loop, and a section that resembles a tRNA anticodon loop called the tle (for tRNA-like element). The adjacent primer-binding site (pbs), comprising a sequence complementary to the 3’ end of the tRNA primer, is followed by a stem-loop structure, sl1, that initiates genome dimerization by hybridizing with sl1 in a second viral RNA molecule to form a “kissing loop,” as illustrated in the box. The sl1, sl2, and sl3 elements are required for efficient viral RNA packaging.

Retroviridae



From Flint et al. *Principles of Virology* (2000), ASM Press

Retrovirus genome

R - Direct repeats at the 5’ and 3’ termini. They are very important during retro-transcription. They contains the polyadenilation signal.

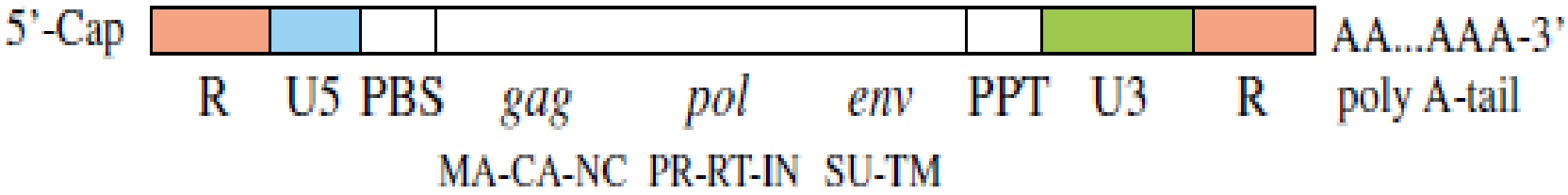
U5 - Non coding, unique sequence at the 5’ end. Important site for the integration process of the proviral DNA

PBS – Primer binding site, 18nt long sequence, anneals to the 3’ end of the cellular tRNA

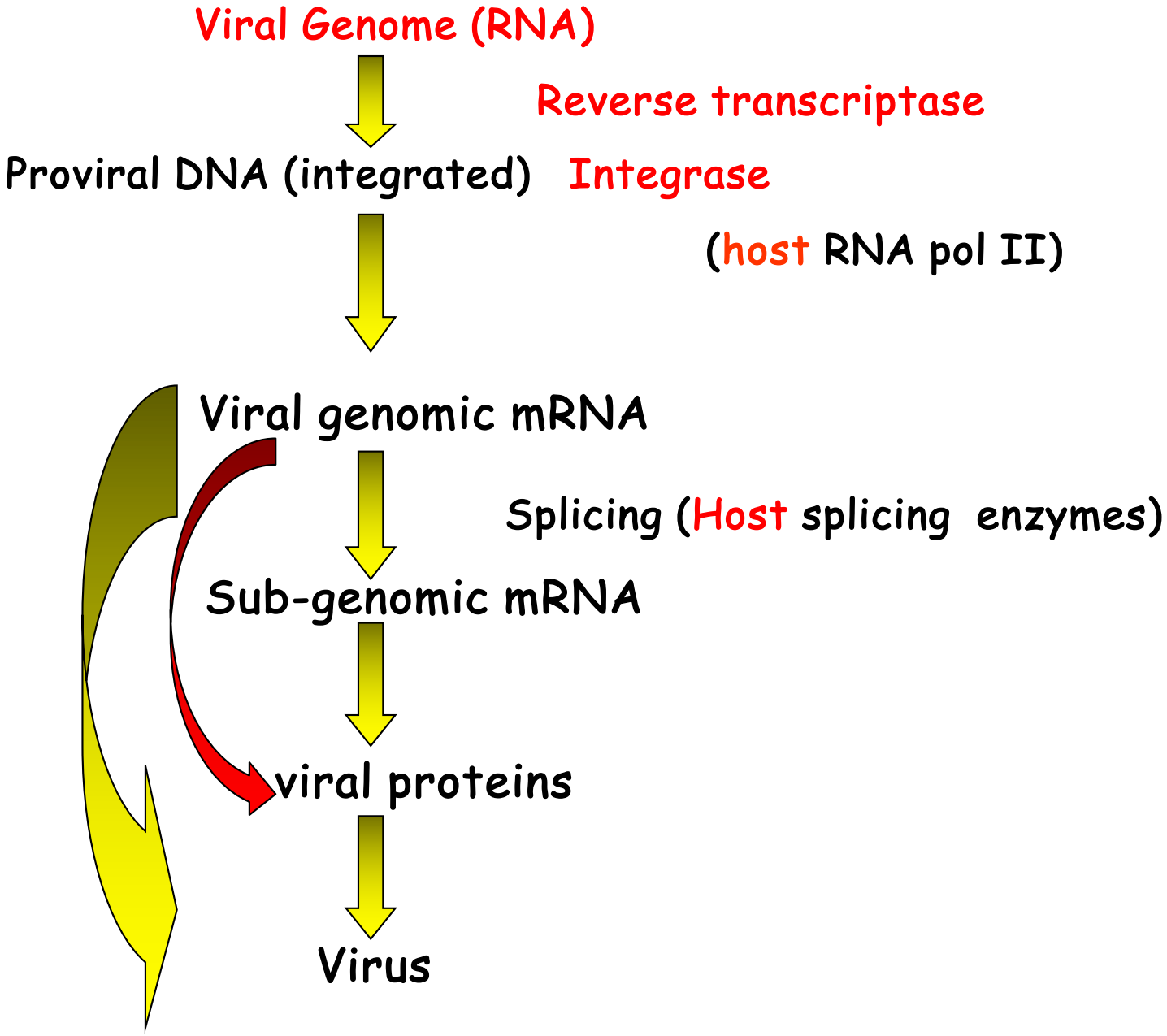
Leader (90-500nt, downstream PBS, not shown), non coding, contains the SD and ψ site

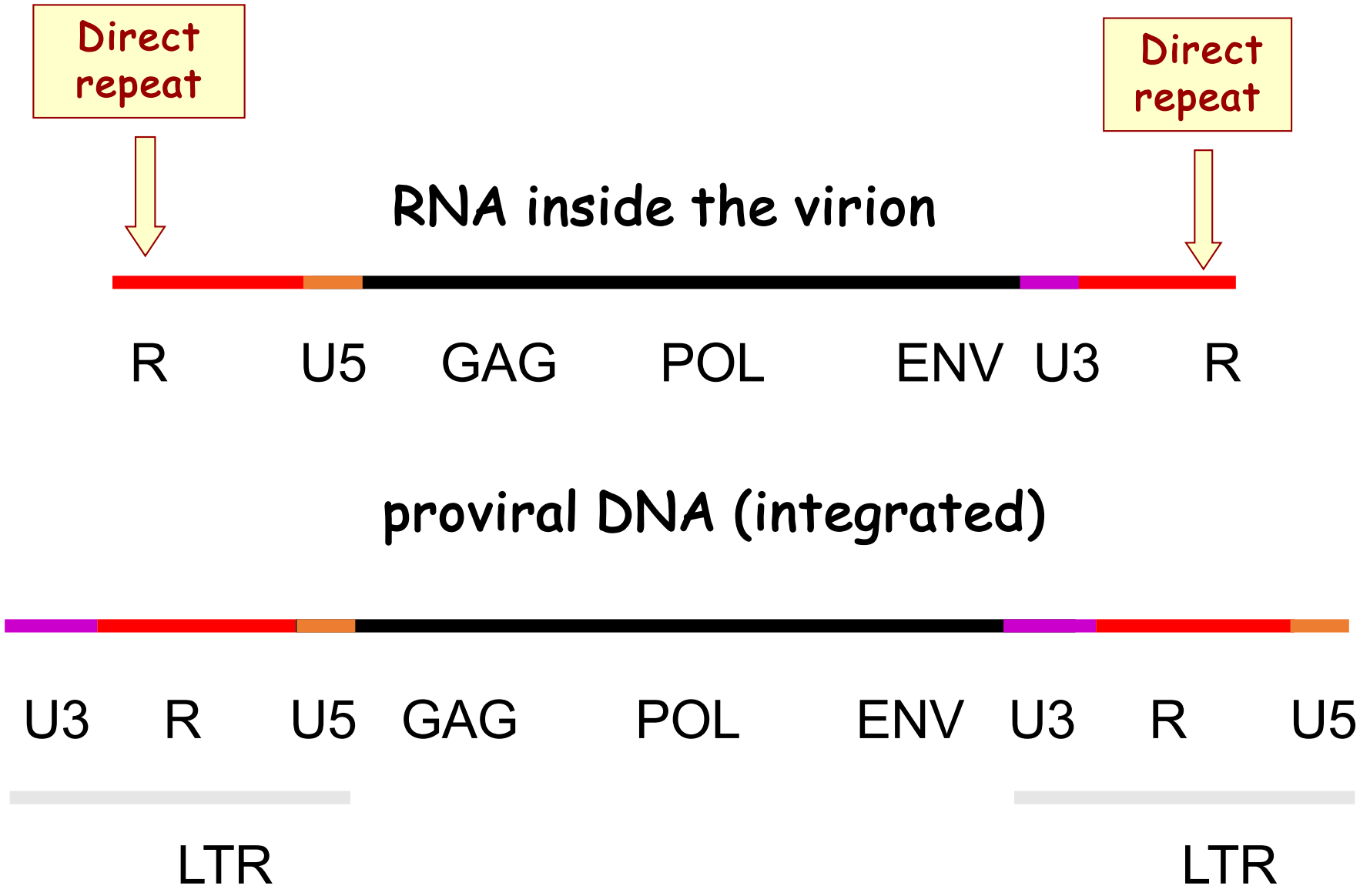
PPT (c.a. 10nt) serves as the primer for the synthesis of the DNA (+) strand

U3 (200-1200nt) Non coding, unique sequence at the 3’ end containing enhancer and promoter elements.

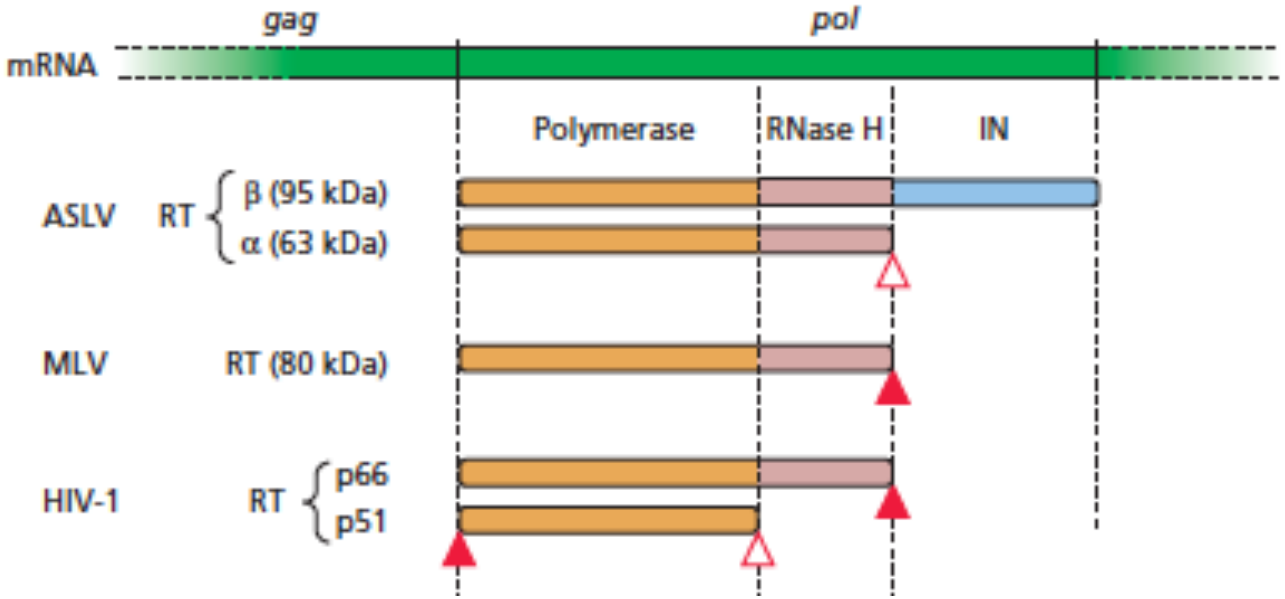


Retrovirus life cycle



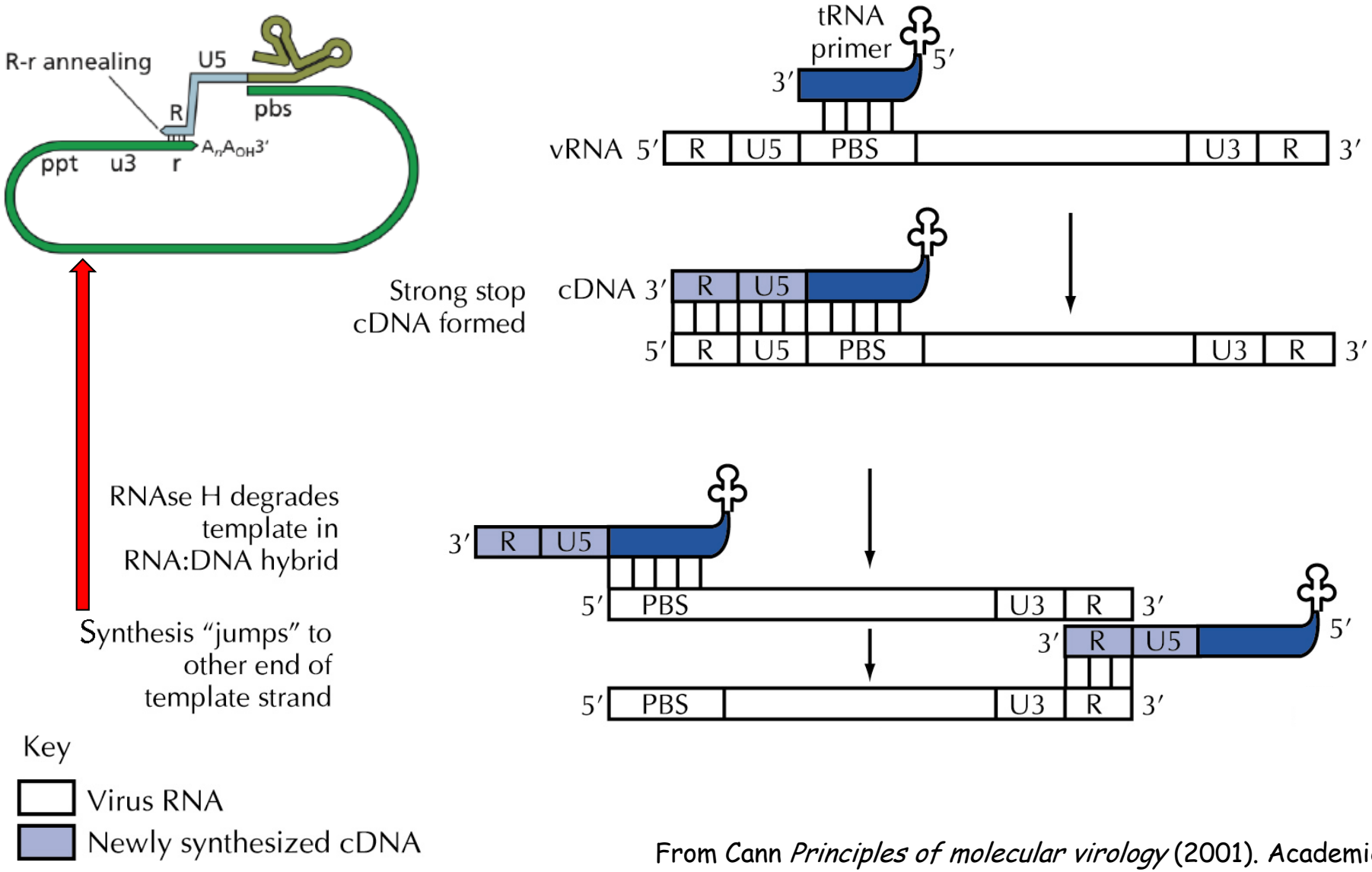

Direct repeat
Direct repeat
RNA inside the virion
R
U5
GAG
POL
ENV
U3
R
proviral DNA (integrated)
U3
R
U5
GAG
POL
ENV
U3
R
U5
LTR
LTR

Reverse transcriptase



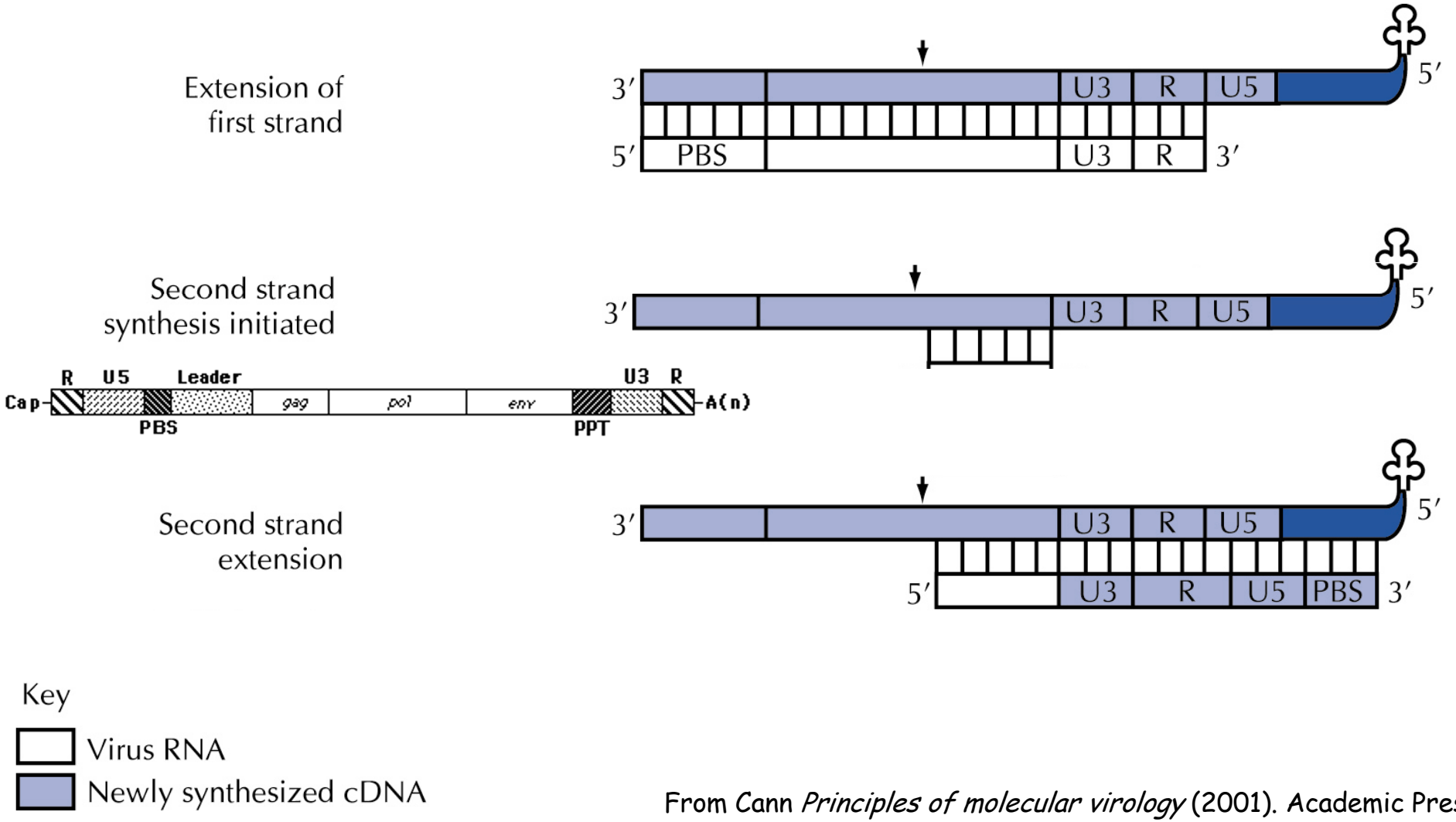
Domain and subunit relationships of the RTs of different retroviruses.
The organization of open reading frames in the mRNAs is indicated at the top. Protein products (not to scale) are shown below, with arrows pointing to the sites of proteolytic processing that produce the diversity of RT subunit composition. Open red arrows indicate partial (asymmetric) processing, and solid red arrows indicate complete processing. ASLV, the alpharetrovirus avian sarcoma/leukosis virus; MLV, the gammaretrovirus murine leukemia virus; HIV-1, the lentivirus human immunodeficiency virus type 1.

Reverse transcription (1)



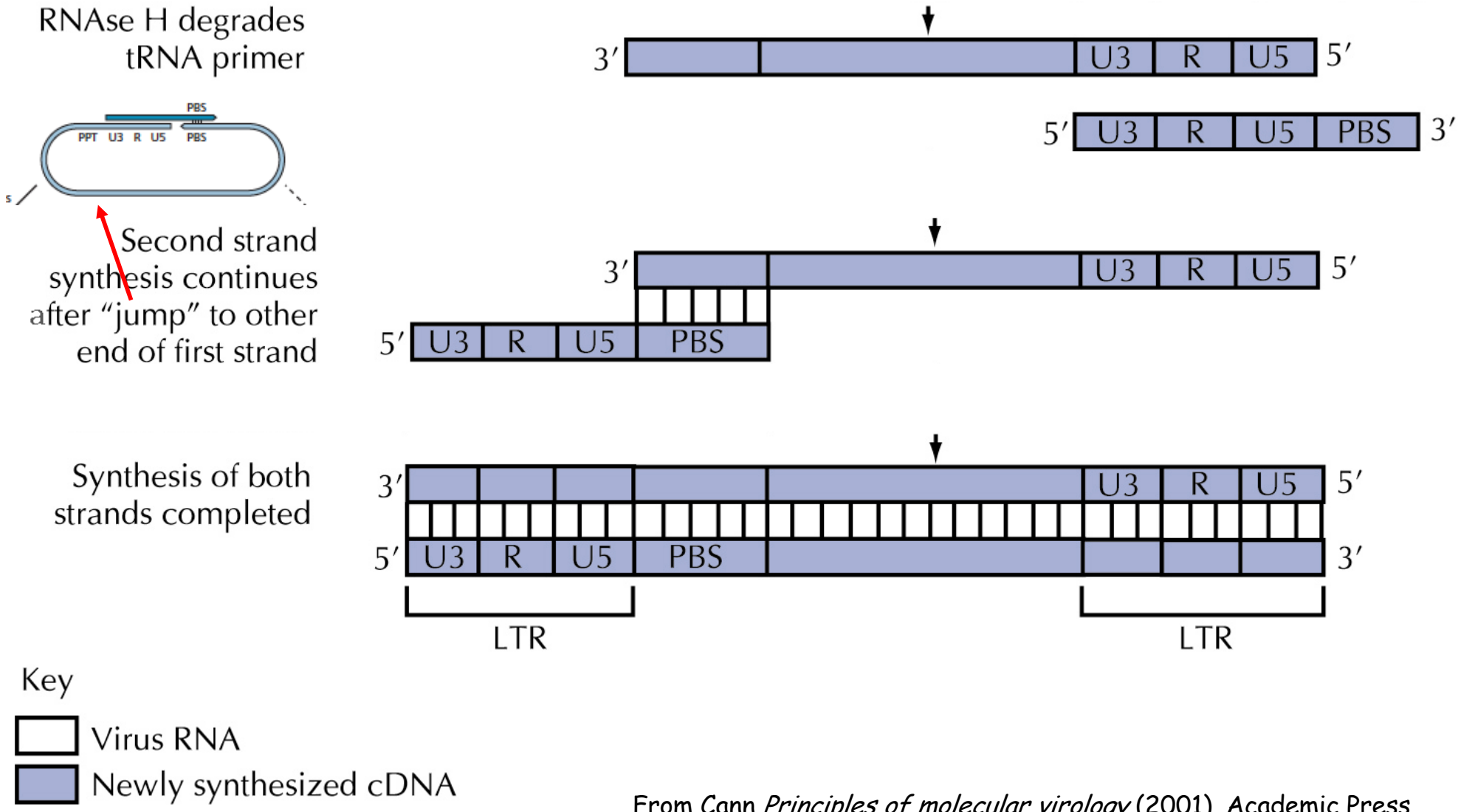
From Cann *Principles of molecular virology* (2001). Academic Press

Reverse transcription (2)

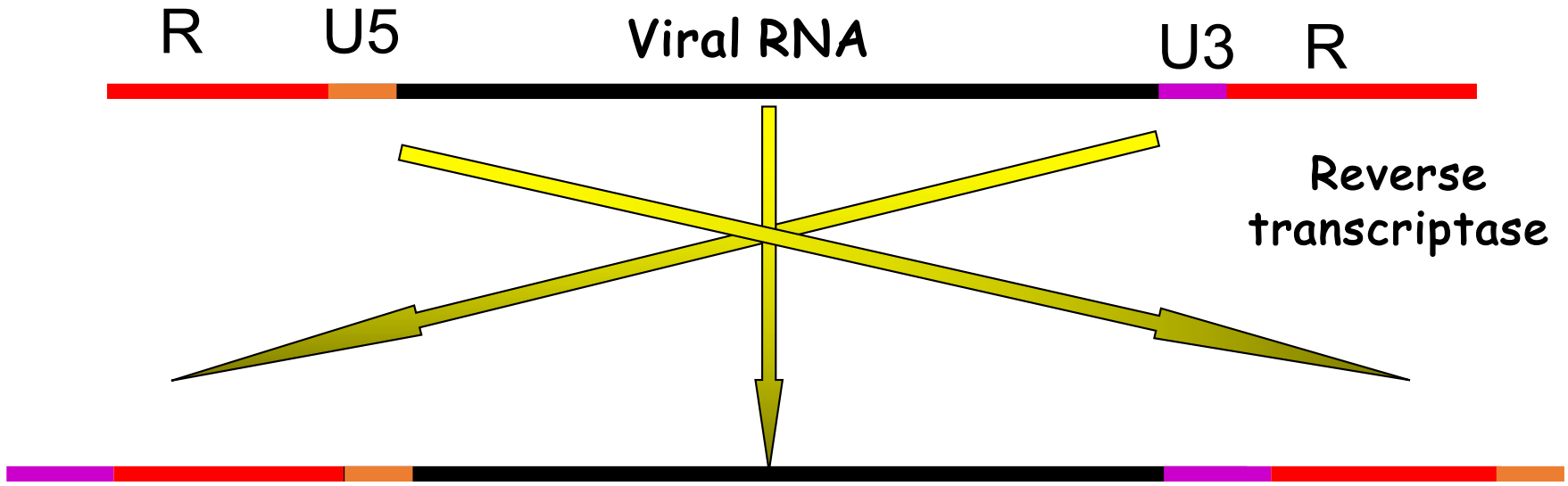


From Cann *Principles of molecular virology* (2001). Academic Press

Reverse transcription (3)

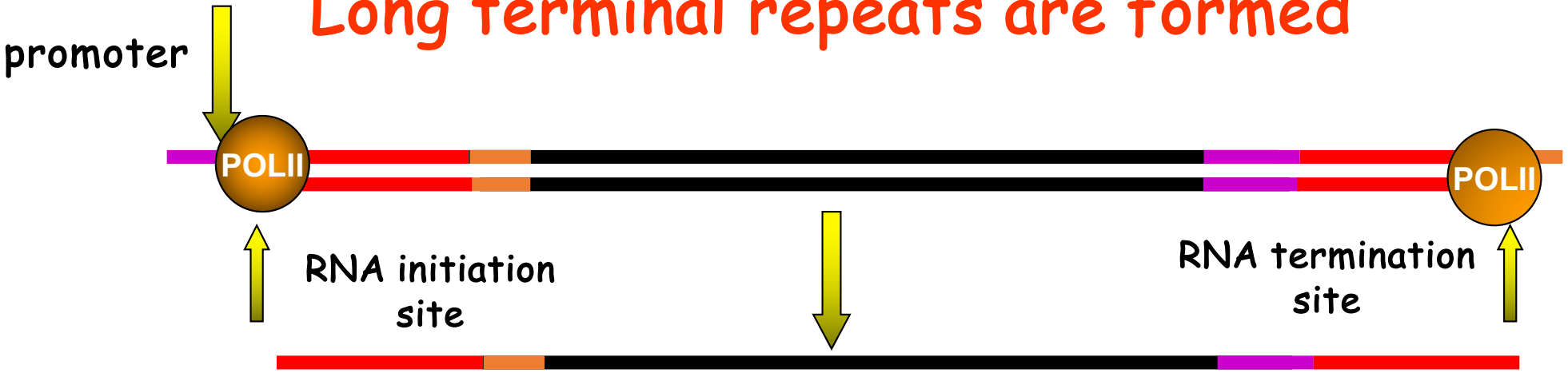


From Cann *Principles of molecular virology* (2001). Academic Press

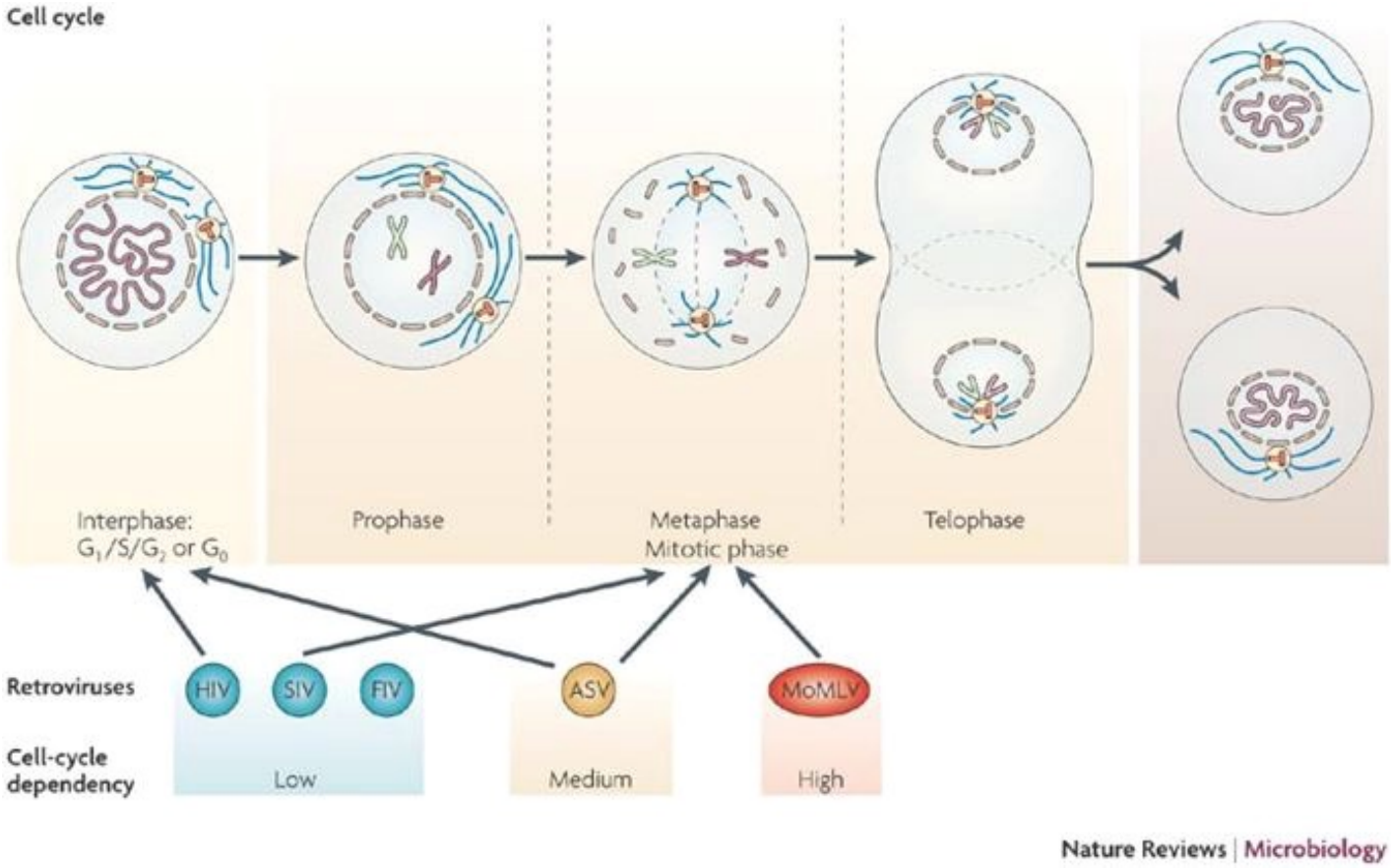


U3 R U5 U3 R U5

Long terminal repeats are formed

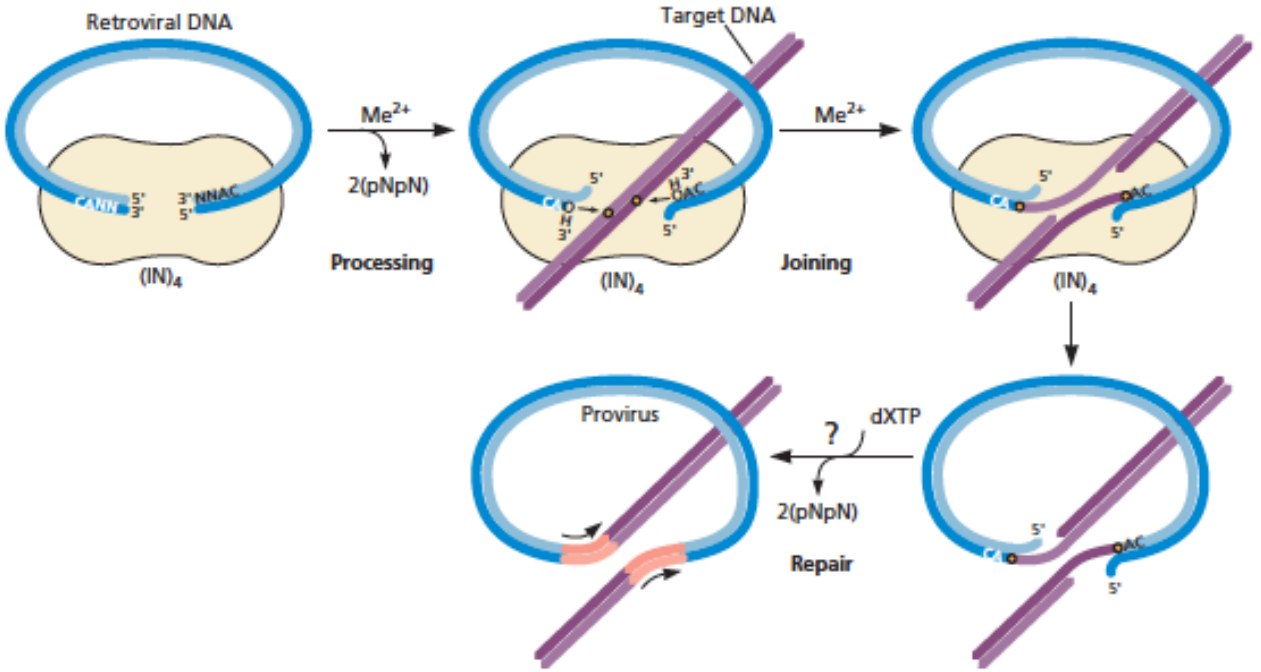


Proviral DNA nuclear entry



The nuclear envelope is intact during interphase. During cell division (mitotic phase), the nuclear envelope completely breaks down at metaphase and is re-formed at telophase. Whereas Moloney murine leukaemia virus (MoMLV) requires the disassembly of the nuclear envelope at mitosis to enter the nucleus, lentiviruses (human, feline and simian immunodeficiency viruses; HIV, SIV and FIV) and some other retroviruses (avian sarcoma virus, ASV) can cross the intact nuclear envelope during interphase.

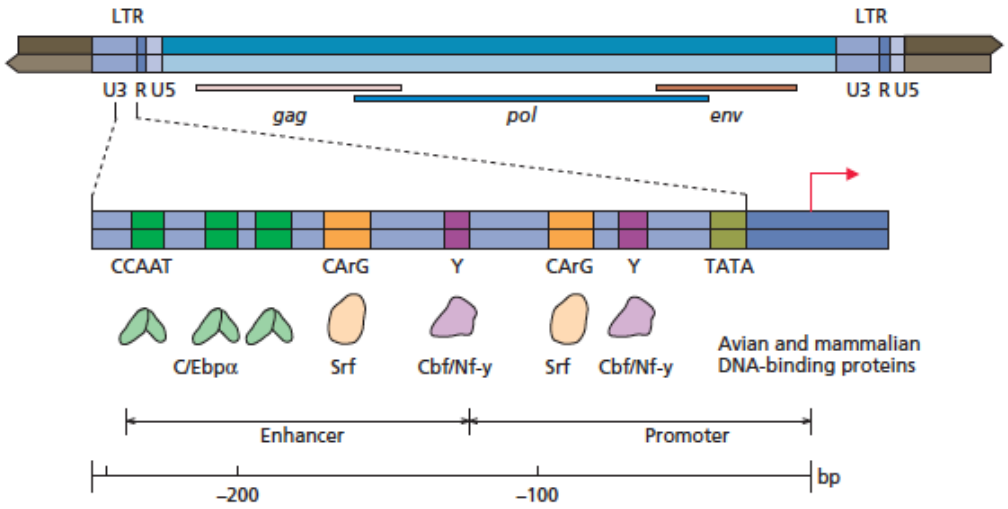
Proviral DNA integration



Three steps in the retroviral DNA integration process. Endonucleolytic nicking adjacent to the conserved dinucleotide near each DNA end results in the removal of a terminal dinucleotide, and formation of a new, recessed CAOH-3' end that will be joined to target DNA in the second step of the IN-catalyzed reaction. Both processing and joining reactions require a divalent metal, Mg2+ or Mn2+. The viral DNA ends are bound by a tetramer of IN protein, (IN)4, and the complex is called an intasome. Results of site-directed mutagenesis of viral DNA ends established that the conserved CAOH-3' dinucleotide is essential for correct and efficient integration. The small gold circles represent the phosphodiester bonds cleaved and re-formed in the joining reaction. The final step in the integration process is a host cell-mediated repair process.

From Flint et al. *Principles of Virology* (2015), ASM Press

Retrovirus expression

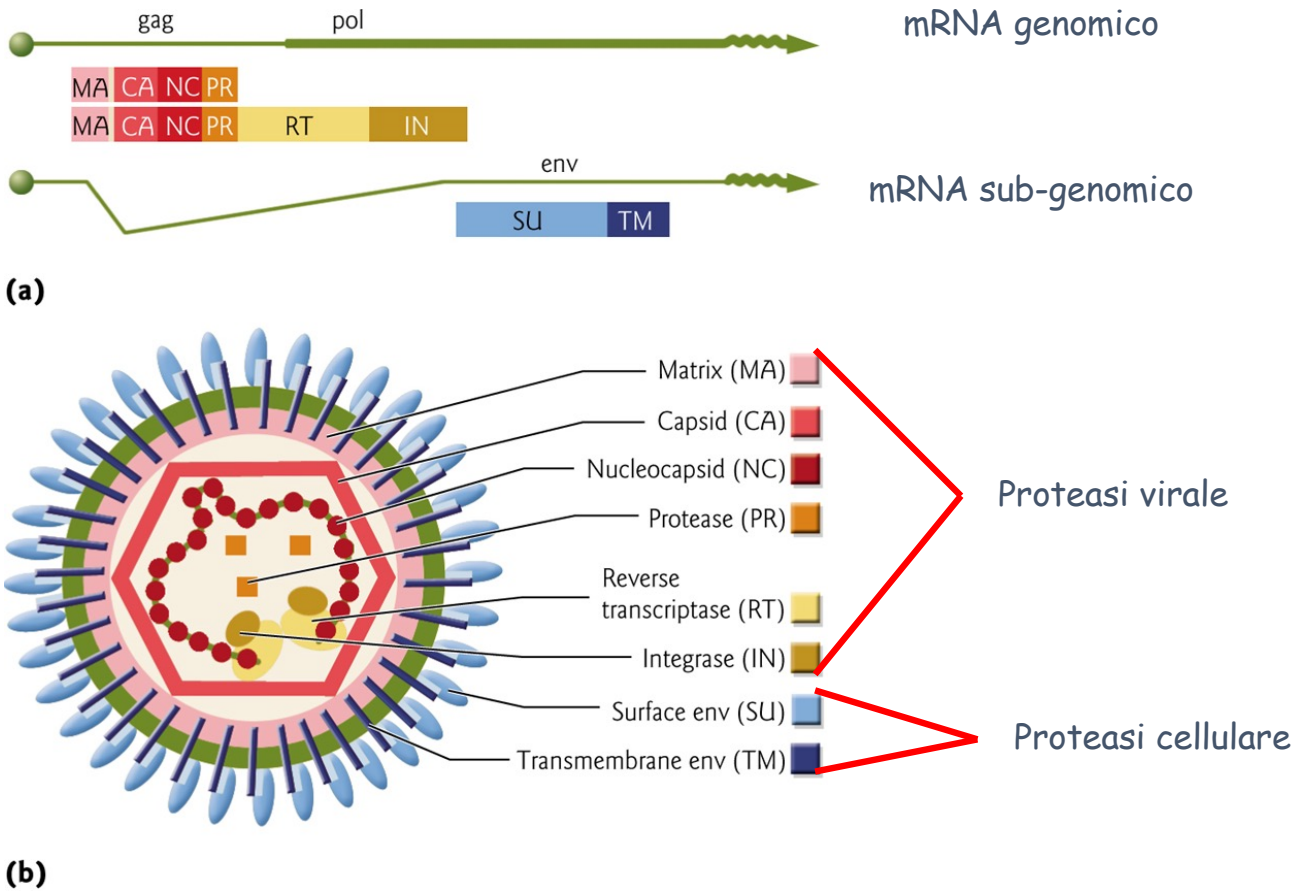


The proviral DNA of an avian leukosis virus is shown at the top. The enhancer and promoter present in the U3 regions of the LTRs are drawn to scale below. Each of the multiple CCAAT, CArG, and Y box sequences, which are required for maximally efficient transcription, is recognized by the proteins listed below, which are present in both avian and mammalian cells. Nf-y, nuclear transcription factor Y; Srf, serum response factor.

Because the LTRs are direct repeats of one another, transcription directed by the 3' LTR extends into cellular DNA and cannot contribute to the expression of retroviral genetic information. In fact, the transcriptional control region of the 3' LTR is normally inactivated by a process called promoter occlusion: the passage of transcribing complexes initiating at the 5' LTR through the 3' LTR prevents recognition of the latter by enhancer- and promoter-binding proteins. Occasionally, transcription from the 3' LTR does occur, with profound consequences for the host cell.

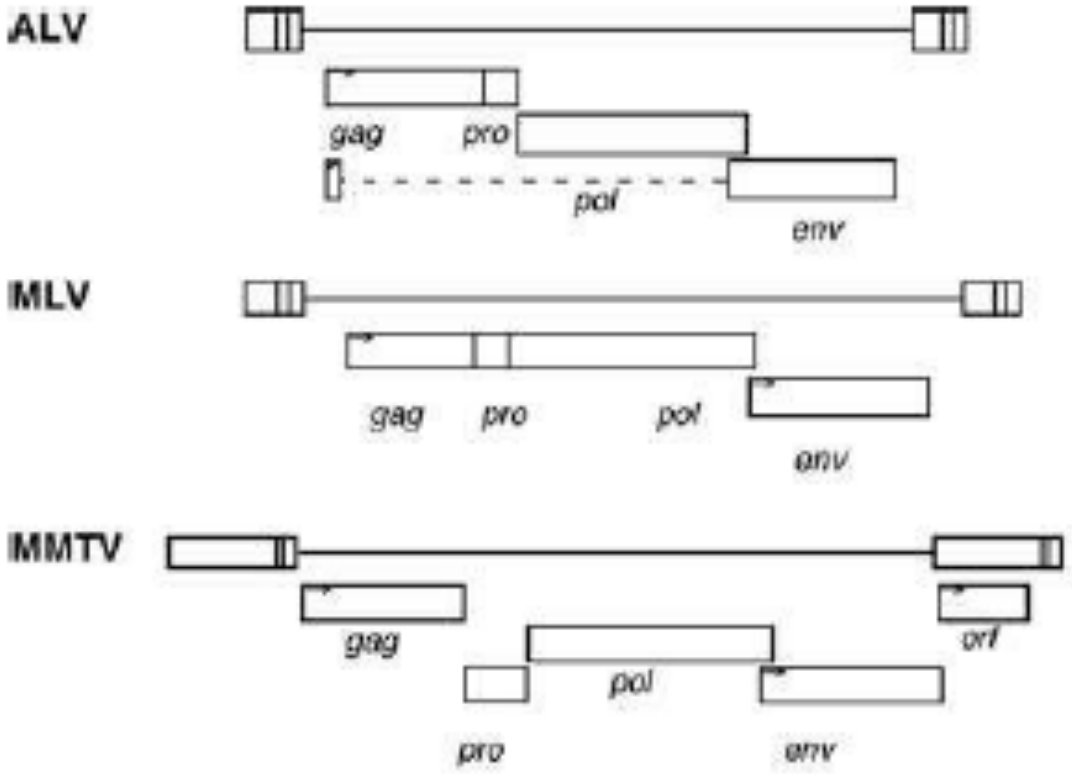
From Flint et al. *Principles of Virology* (2015), ASM Press

Retrovirus expression



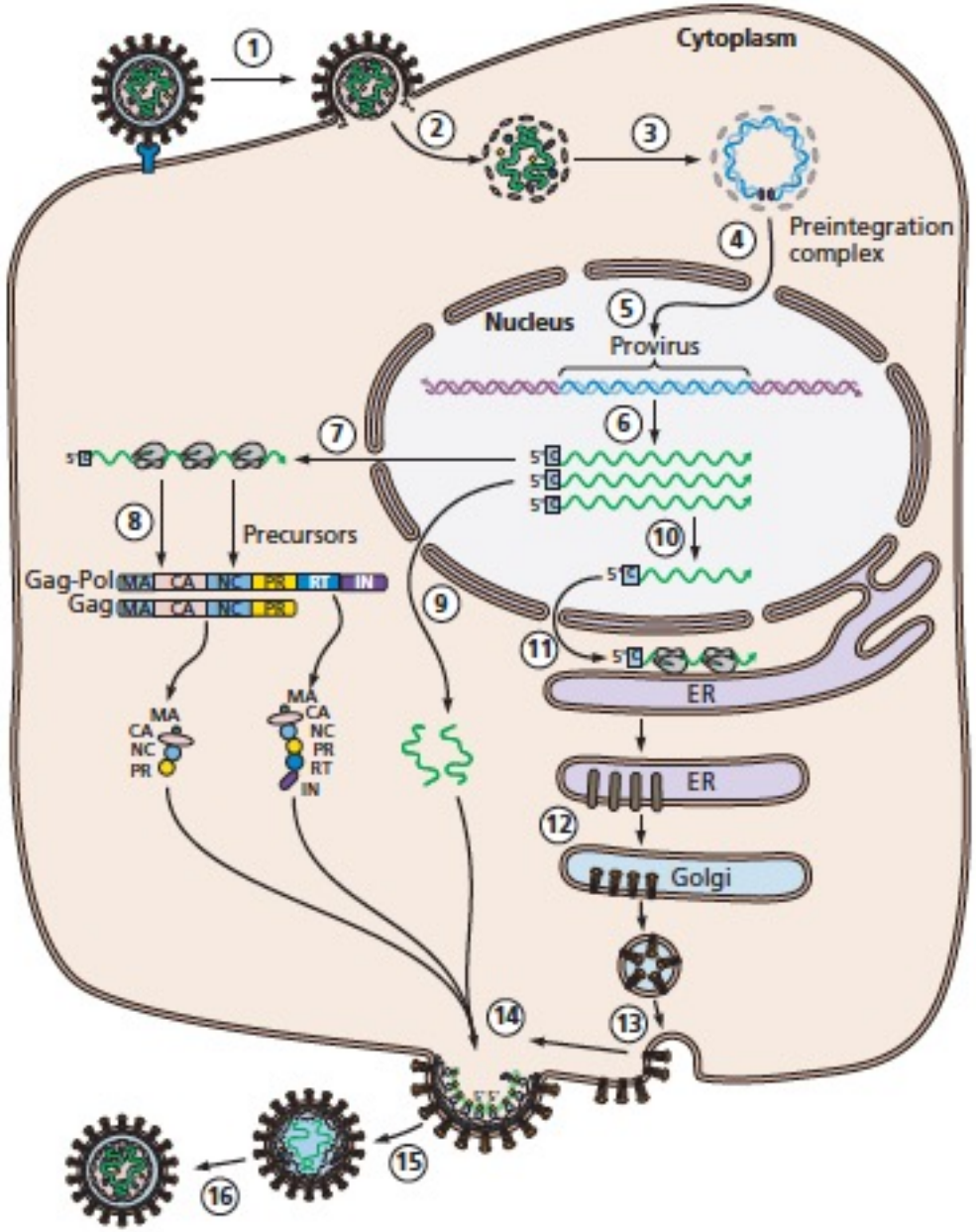
From Dimmock, Easton and Leppard, "Introduction to Modern *Virology*" (2016). Blackwell Publishing

Retrovirus expression



For the alpharetroviruses, *gag* and *pro* are fused and expressed as a single polyprotein*; pol* is in a different reading frame, and a frameshift is used to express the Gag-Pro-Pol polyprotein.
For the gammaretroviruses, *gag and a pro-pol* fusion are in the same reading frame and separated by a stop codon, and translational readthrough is used to make Gag-Pro-Pol.
For the betaretroviruses *gag, pro, and pol* are all in different frames and successive frameshifts are used to express Gag-Pro and Gag-Pro-Pol polyproteins.

Retrovirus life cycle



From Flint et al. *Principles of Virology* (2015), ASM Press

Retrovirus life cycle

Single-cell reproductive cycle of a retrovirus with a simple genome. (1) The virus attaches by binding of the viral envelope protein to specific receptors on the surface of the cell. The identities of receptors are known for many retroviruses. (2) The viral core is deposited into the cytoplasm following fusion of the virion and cell membranes. Entry of some beta- and gammaretroviruses may occur via the endocytic pathways. (3) The viral RNA genome is reverse transcribed by the virion reverse transcriptase (RT) within a subviral particle. The product is a linear double-stranded viral DNA with ends that are shown juxtaposed in preparation for integration. (4) Viral DNA and integrase (IN) protein gain access to the nucleus with the help of intracellular trafficking machinery or, in some cases, by exploiting nuclear disassembly during mitosis. (5) Integrative recombination, catalyzed by IN, results in site-specific insertion of the viral DNA ends, which can take place at many locations in the host genome, with distinct, characteristic general preferences for different viral IN proteins. (6) Transcription of integrated viral DNA (the provirus) by the host cell RNA polymerase II system produces full-length RNA transcripts. (7) Some full-length RNA molecules are exported from the nucleus to the cytoplasm and serve as mRNAs. (8) These mRNAs are translated by cytoplasmic ribosomes to form the viral Gag and Gag-Pol polyprotein precursors at a ratio of approximately 10:1.

Retrovirus life cycle

(9) Some full-length RNA molecules are destined to become encapsidated as progeny viral genomes. The mechanism for sequestering RNAs for this purpose is unknown, but there is evidence that a fraction of the ASV Gag protein traffics through the nucleus, where it could perform this function. (10) Other full-length RNA molecules are spliced within the nucleus to form mRNA for the Env polyprotein. (11) Env mRNA is translated by ribosomes bound to the endoplasmic reticulum (ER). (12) The Env proteins are transported through the Golgi apparatus, where they are glycosylated and cleaved by cellular enzymes to form the mature SU-TM complex. (13) Mature envelope proteins are delivered to the surface of the infected cell. (14) Virion components (two copies of the viral RNA, Gag and Gag-Pol precursors, and SU-TM) assemble at budding sites with the help of cis-acting signals encoded in each. Type C retroviruses (e.g., alpharetroviruses and lentiviruses) assemble at the inner face of the plasma membrane, as illustrated. Other types (A, B, and D) assemble on internal cellular membranes. (15) The nascent particles bud from the surface of the cell.
(16) Maturation (and infectivity) requires the action of the virus-encoded protease (PR), which is itself a component of the core precursor polyprotein. During or shortly after budding, PR cleaves at specific sites within the Gag and Gag-Pol precursors to produce the mature viral proteins. This process causes a characteristic condensation of the virus cores.