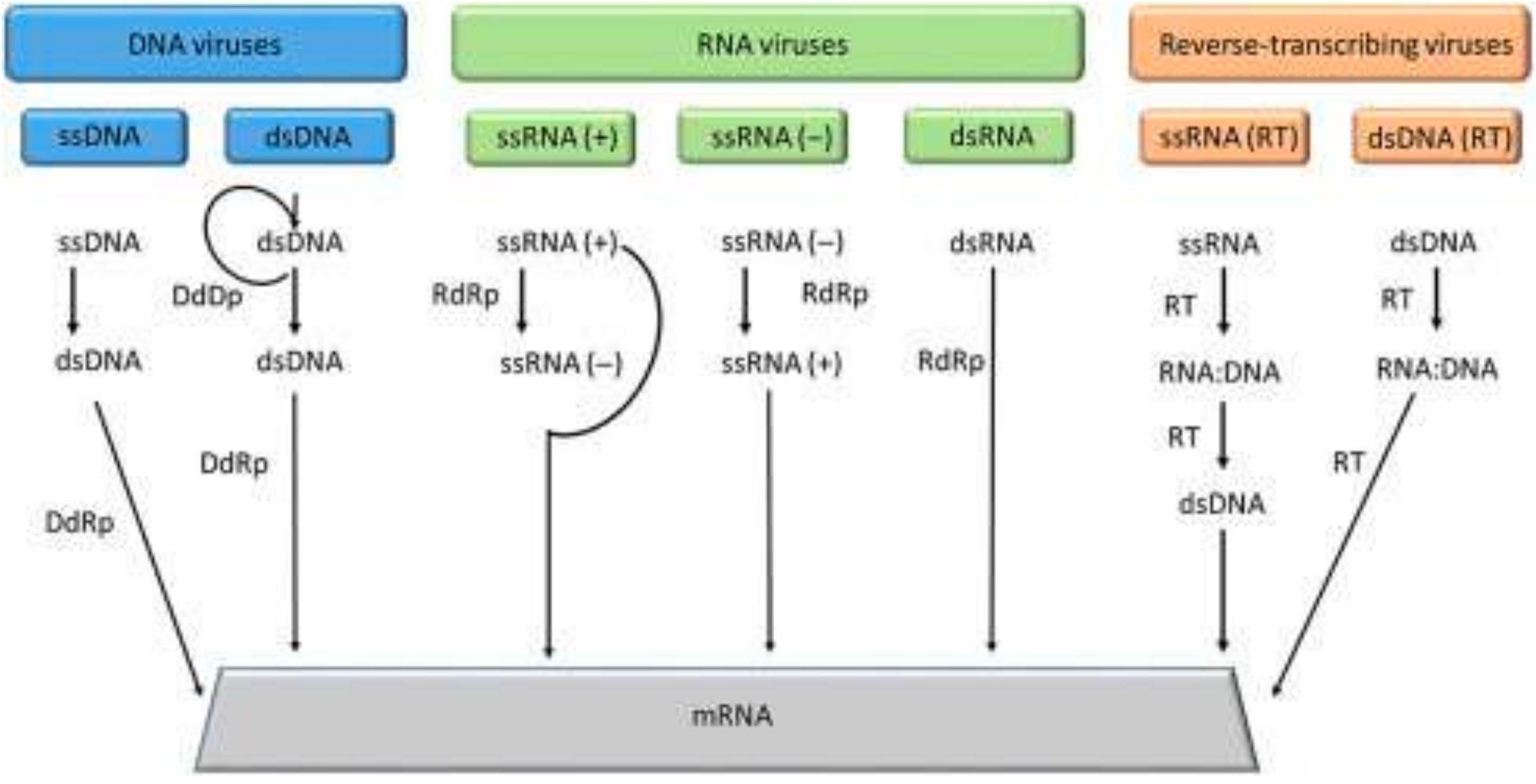
L04c

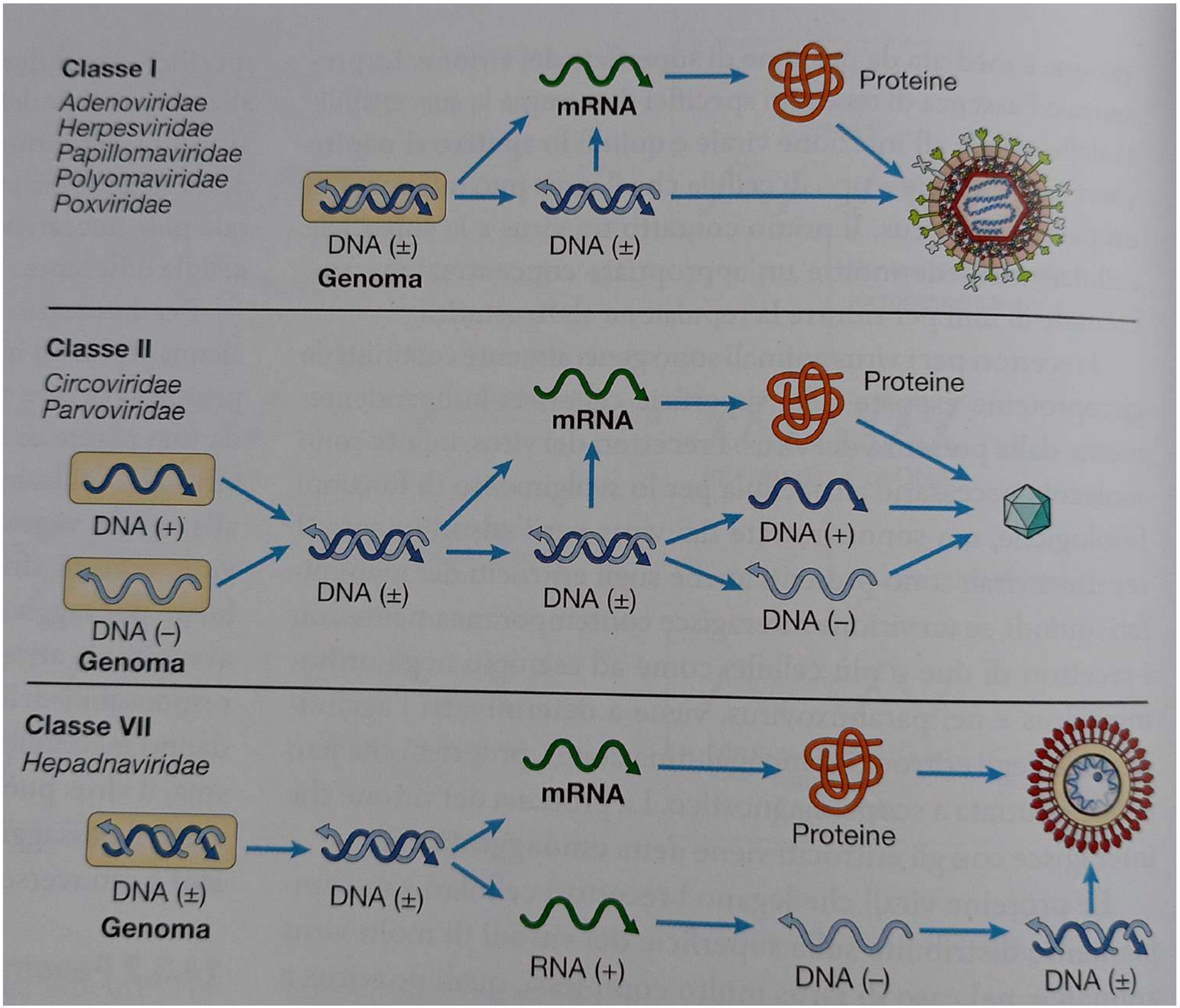
Recap

Summary of replication and transcription modes of different classes of viruses



Rampersad & Tennants, 2018

DdDp, DNA-dependent DNA polymerase; DdRp, DNA-dependent RNA polymerase; RdRP, RNA- dependent RNA polymerase; RT, reverse transcriptase. The ssRNA(+) can serve as the template for translation and does not undergo any modification prior to translation.


Classe I
Adenoviridae
Herpesviridae
Papillomaviridae
Polyomaviridae
Poxviridae
mRNA
Proteine
DNA (±)
Genoma
DNA (±)
Classe II
Circoviridae
Parvoviridae
mRNA
Proteine
DNA (+)
DNA (–)
Genoma
DNA (±)
DNA (±)
DNA (+)
DNA (–)
Classe VII
Hepadnaviridae
mRNA
Proteine
DNA (±)
Genoma
DNA (±)
RNA (+)
DNA (–)
DNA (±)


Biologia dei microrganismi
terza edizione
a cura di
Gianni Dehò e Enrica Galli
con la collaborazione di
Maria Lina Bernardini
Luciano Paolozzi
Anna Maria Puglia
Anna Maria Sanangelantoni
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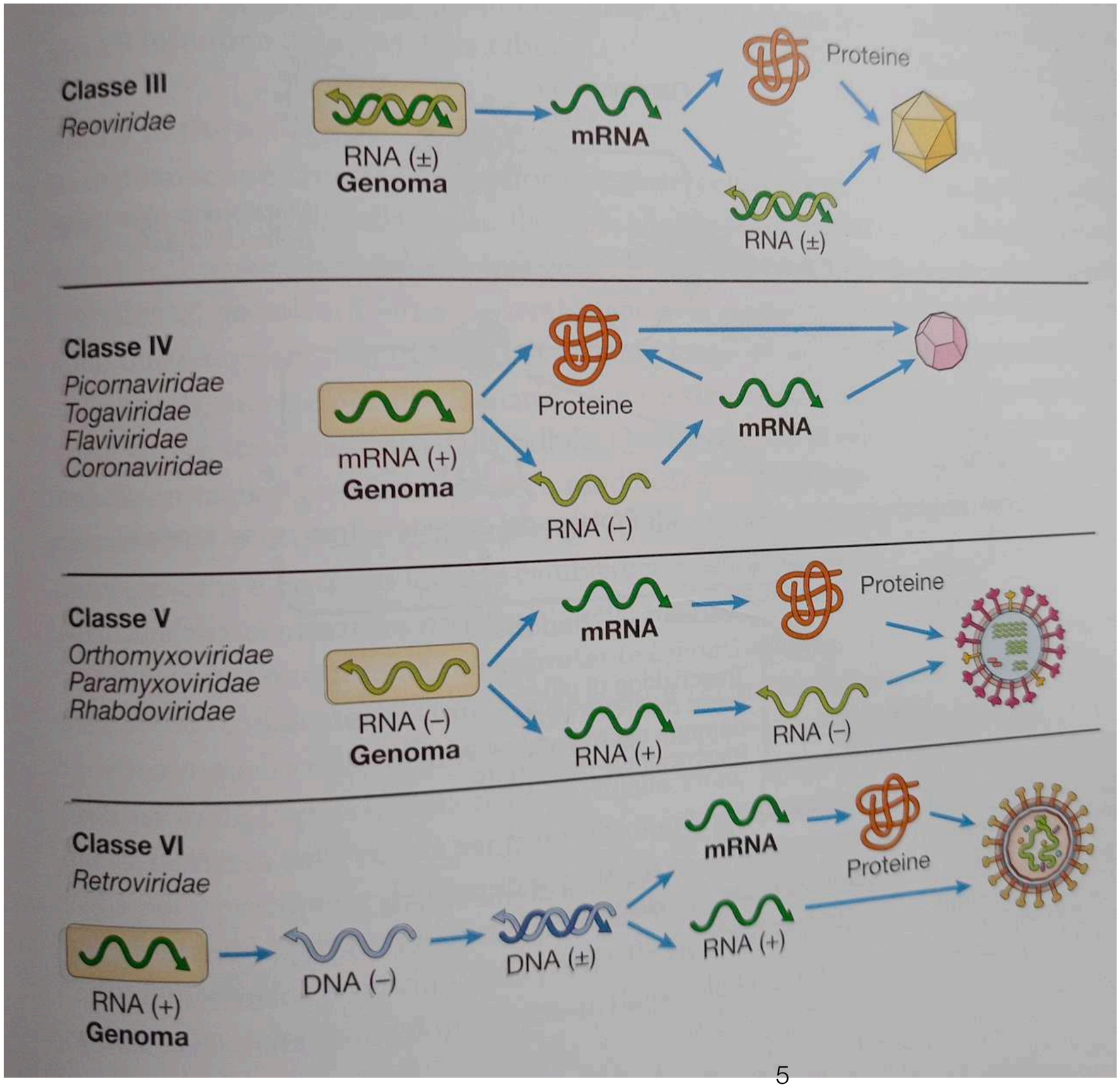
Classe III
Reoviridae
RNA (±)
Genoma
mRNA
Proteine
RNA (±)
Classe IV
Picornaviridae
Togaviridae
Flaviviridae
Coronaviridae
mRNA (+)
Genoma
Proteine
mRNA
RNA (–)
Classe V
Orthomyxoviridae
Paramyxoviridae
Rhabdoviridae
RNA (–)
Genoma
mRNA
Proteine
RNA (+)
RNA (–)
Classe VI
Retroviridae
RNA (+)
Genoma
DNA (–)
DNA (±)
mRNA
Proteine
RNA (+)


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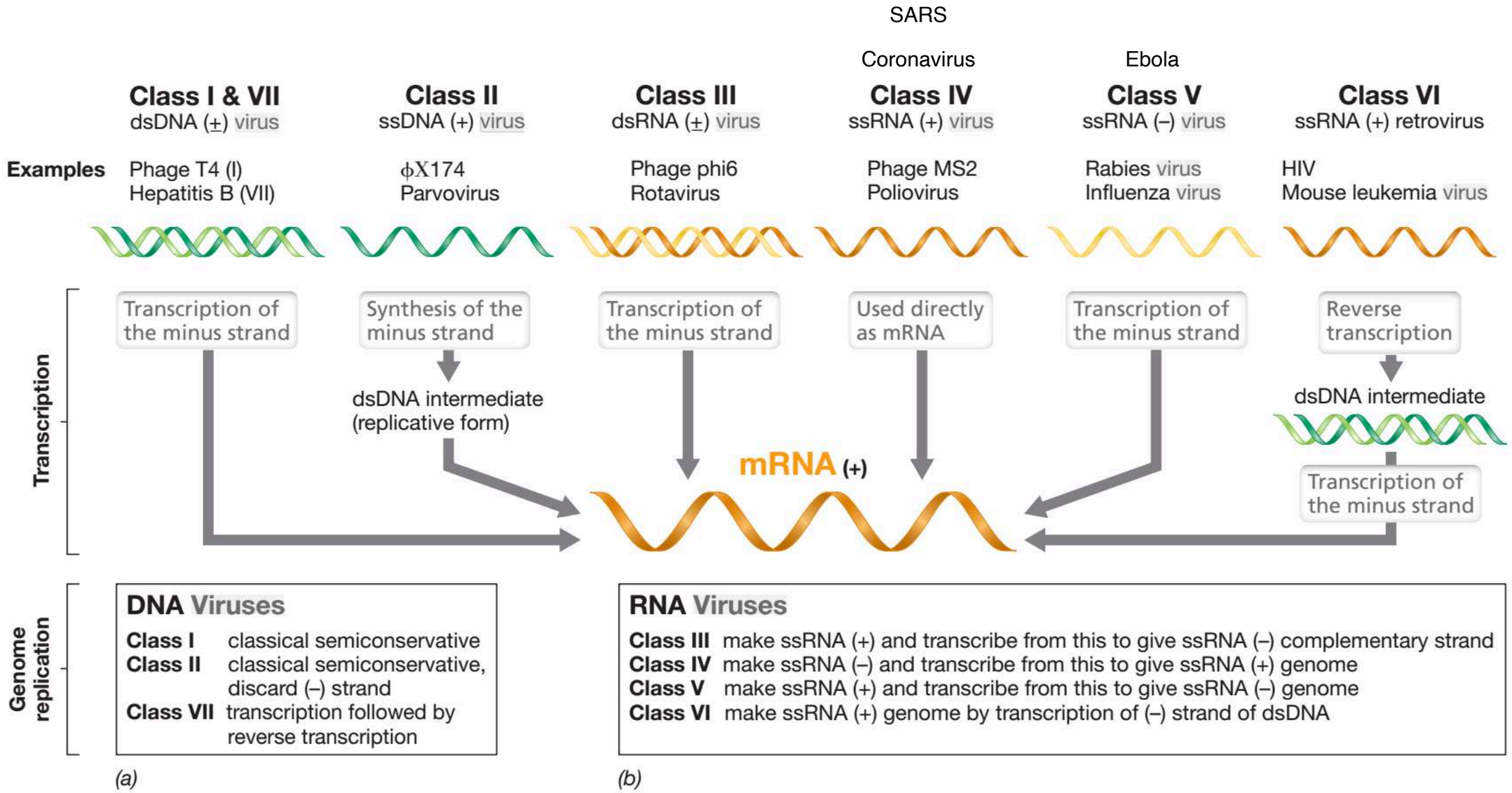
Nucleic acid content

"The Baltimore classification of viral genome"

SARS

Coronavirus

Ebola

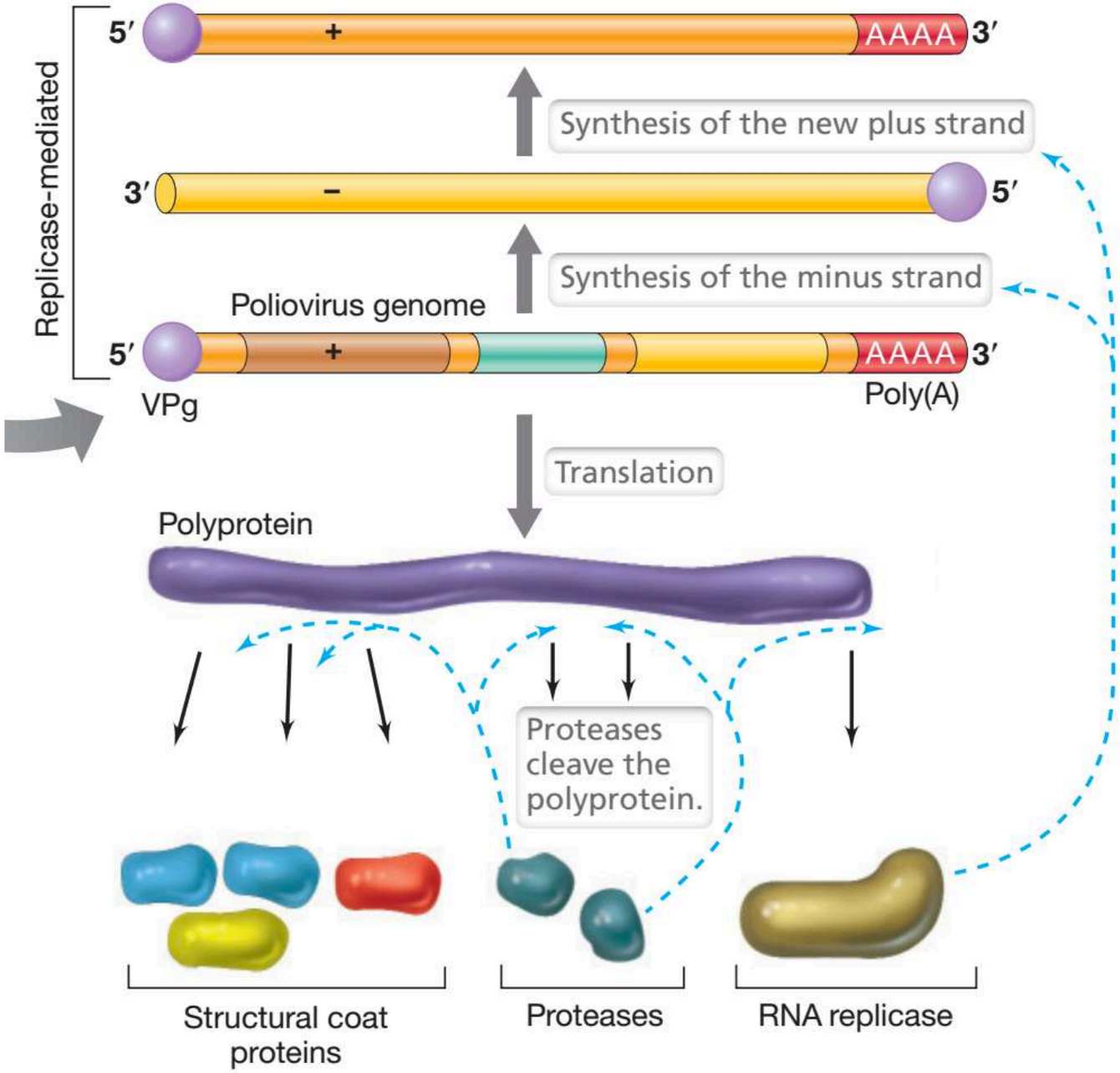


Madigan et al. 2020

- Linear, circular & single stranded genomes
- Plus sense, minus sense in terms of their base sequence
- + configuration have = base sequence as host mRNA —> translation to form viral proteins
- - configuration are complementary in base sequence to viral mRNA

Poliovirus

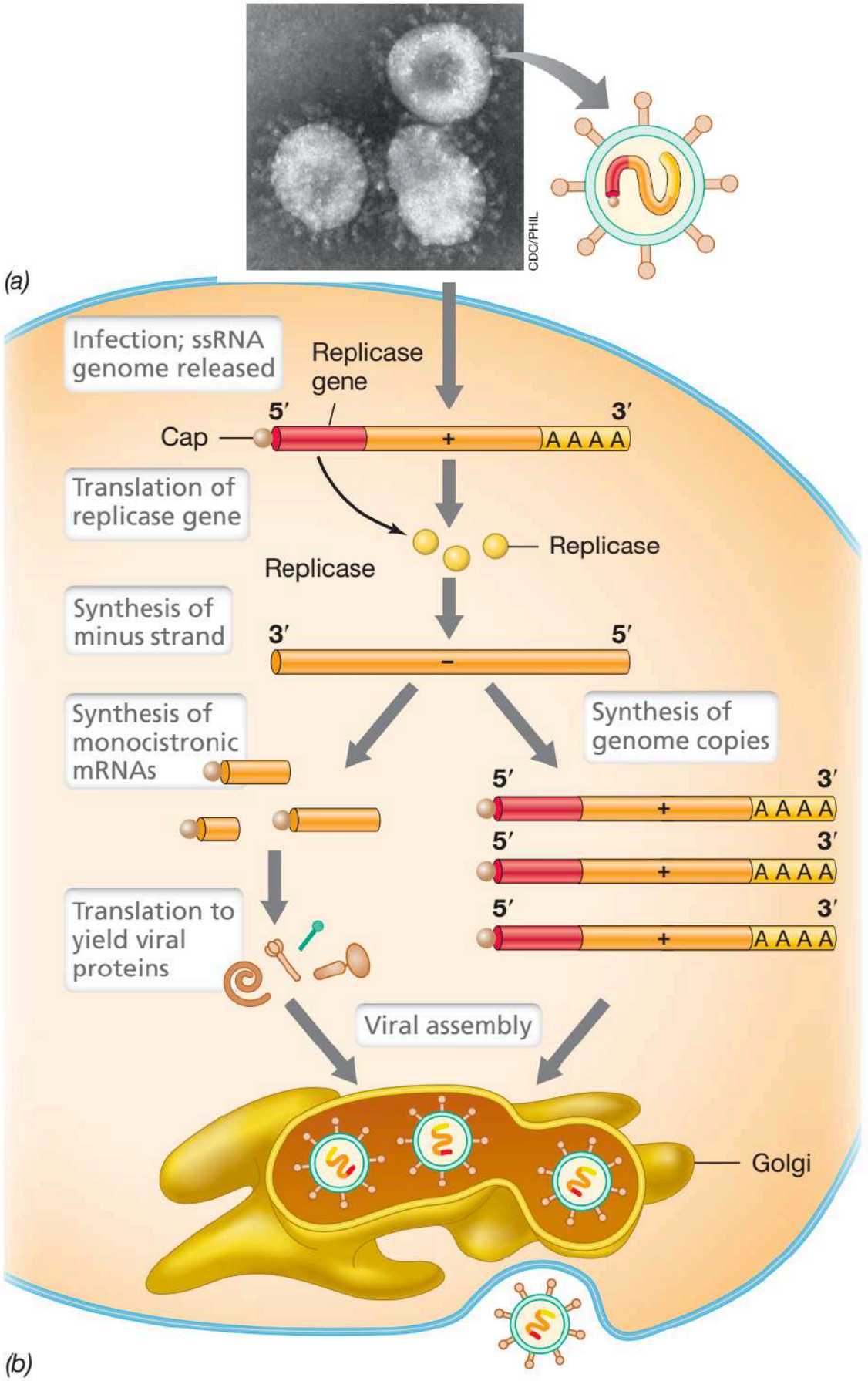
- Positive ssRNA
- 7.4 kb
- At 5′ terminus of viral RNA is a protein, called the **VPg protein**
- VPg protein is **attached covalently** to genomic RNA
- At 3′ terminus is a **poly(A) tail,** a sign of Euk mRNA
- VPg f**acilitate binding to host ribosome tightly**
- Translation yields a **polyprotein**, **a single protein that self-cleaves into several smaller proteins**
- **RNA replicase syntheses RNA- and RNA+**
- 5 hr lytic cycle
- In cytoplasm
- Hotspots in person's throat and intestines
- Spinal cord infection —> paralysis



Madigan et al. 2020

Coronavirus

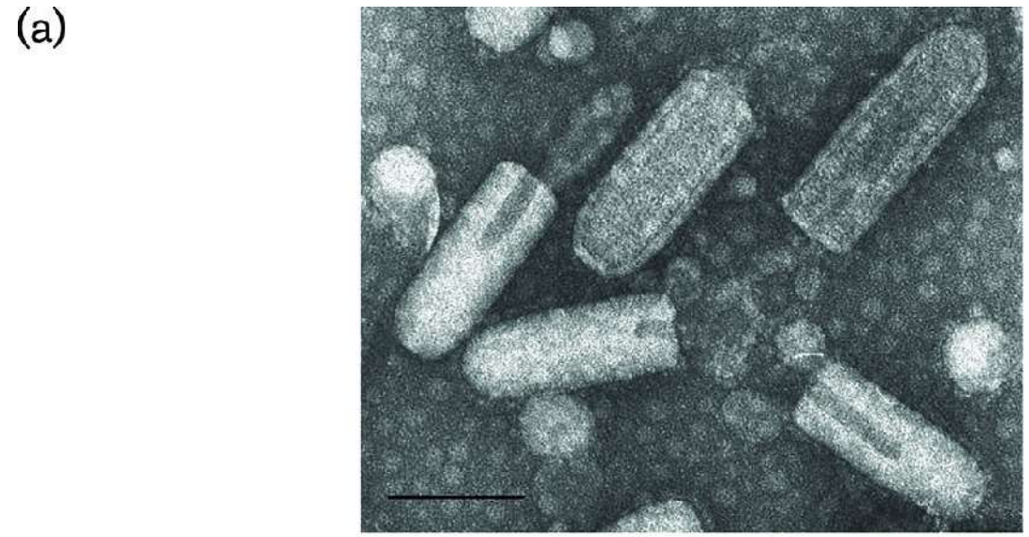
- Coronaviruses single-stranded plus RNA viruses
- ssRNA+—> translate only a few genes: **replicase**
- **Replicase produces - strands for translation of other genes**
- **Replicate in cytoplasm**
- Club-shaped glycoprotein spikes on their surfaces —> crown
- Largest of any known RNA viruses, about **30 kb**
- **Plus sense**, coronavirus genome can **function directly in cell as mRNA**
- **Virions assembled in Golgi complex**

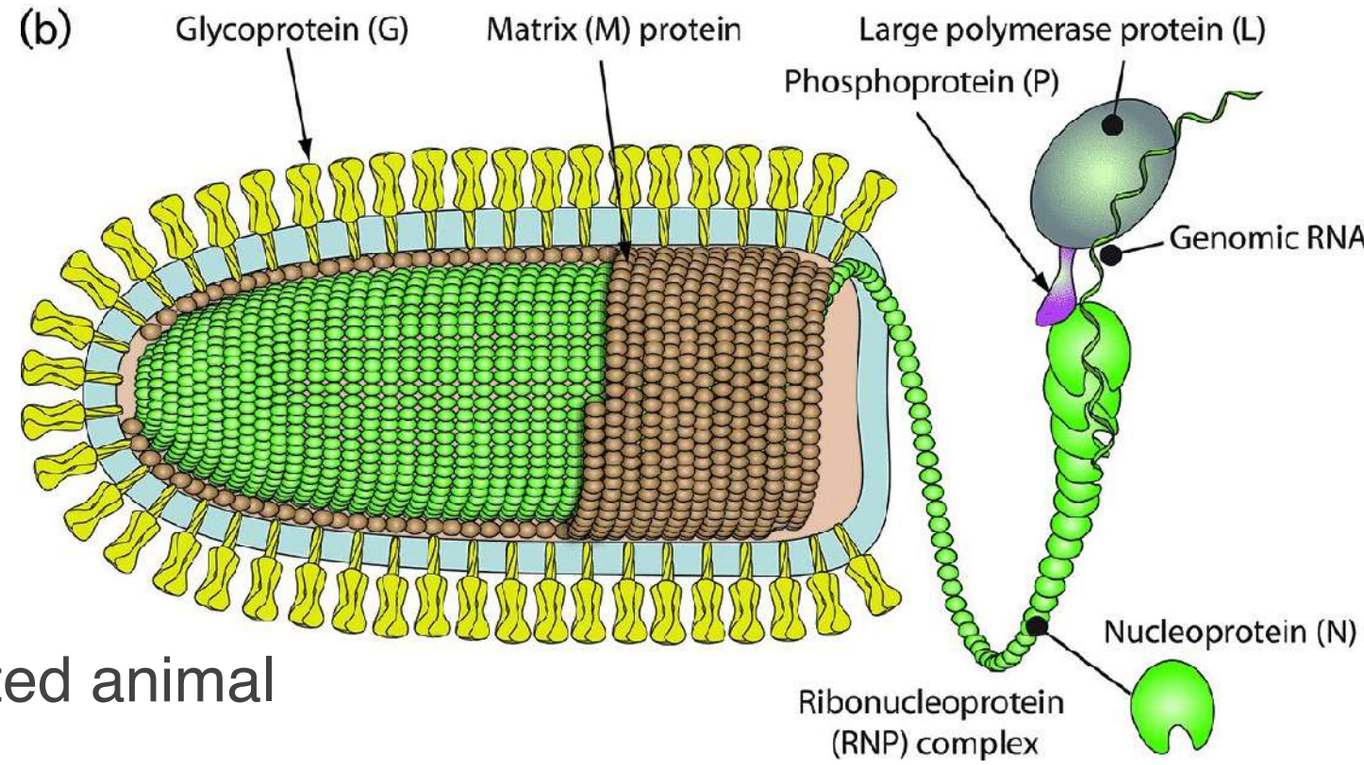


Madigan et al. 2020

Rhabdovirus

- Enveloped virus
- ssRNA -
- Bullet-shape
- Complex structure
- Rabies is a zoonotic disease





- Transmitted via the saliva of an infected animal
- Dogs are the most important reservoir for rabies viruses,
- Dog bites account for >99% of human cases
- Virus first infects peripheral motor neurons, and symptoms occur after the virus reaches the central nervous system

Walker et al., 2018

Rhabdovirus

- Negative-single strand RNA viruses are complementary in base sequence to the mRNA that is formed

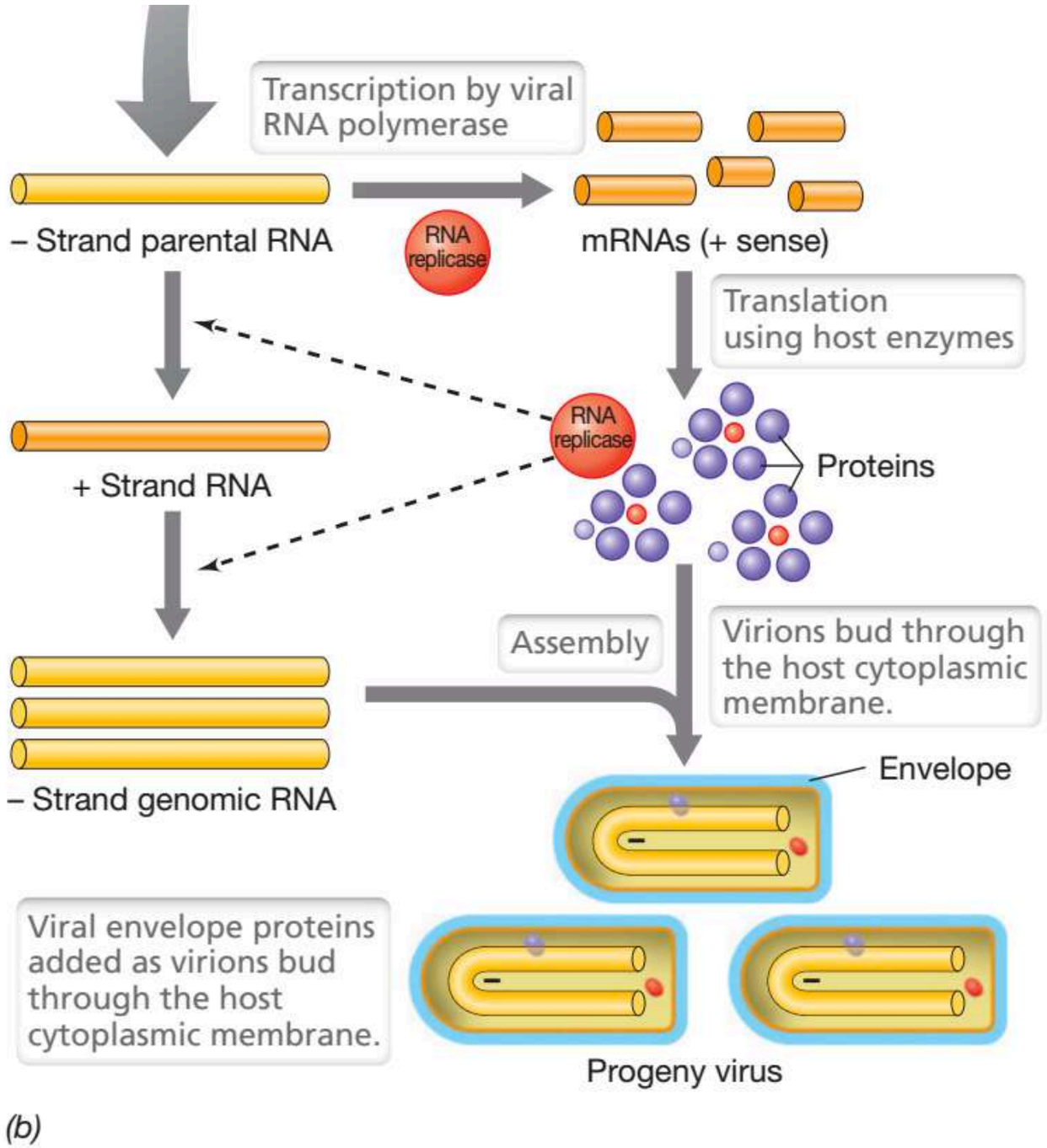
- **Genome is transcribed by the Replicase**

- Transcription in cytoplasm and generates **two classes of RNAs**

- The **first** is a series of mRNAs encoding each of **viral proteins**

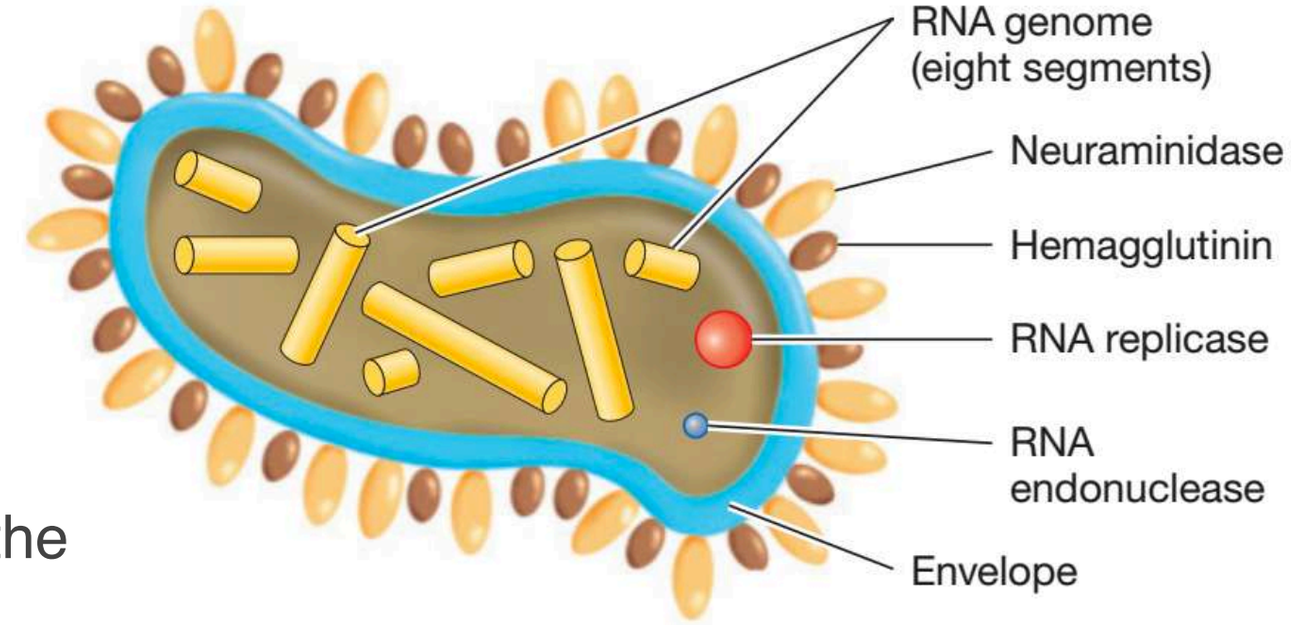
- The **second** is a complementary copy of the entire viral genome (+) —> **functions as a template for synthesis ssRNA (-)**

- **Budding virions from host cytoplasmic membrane**



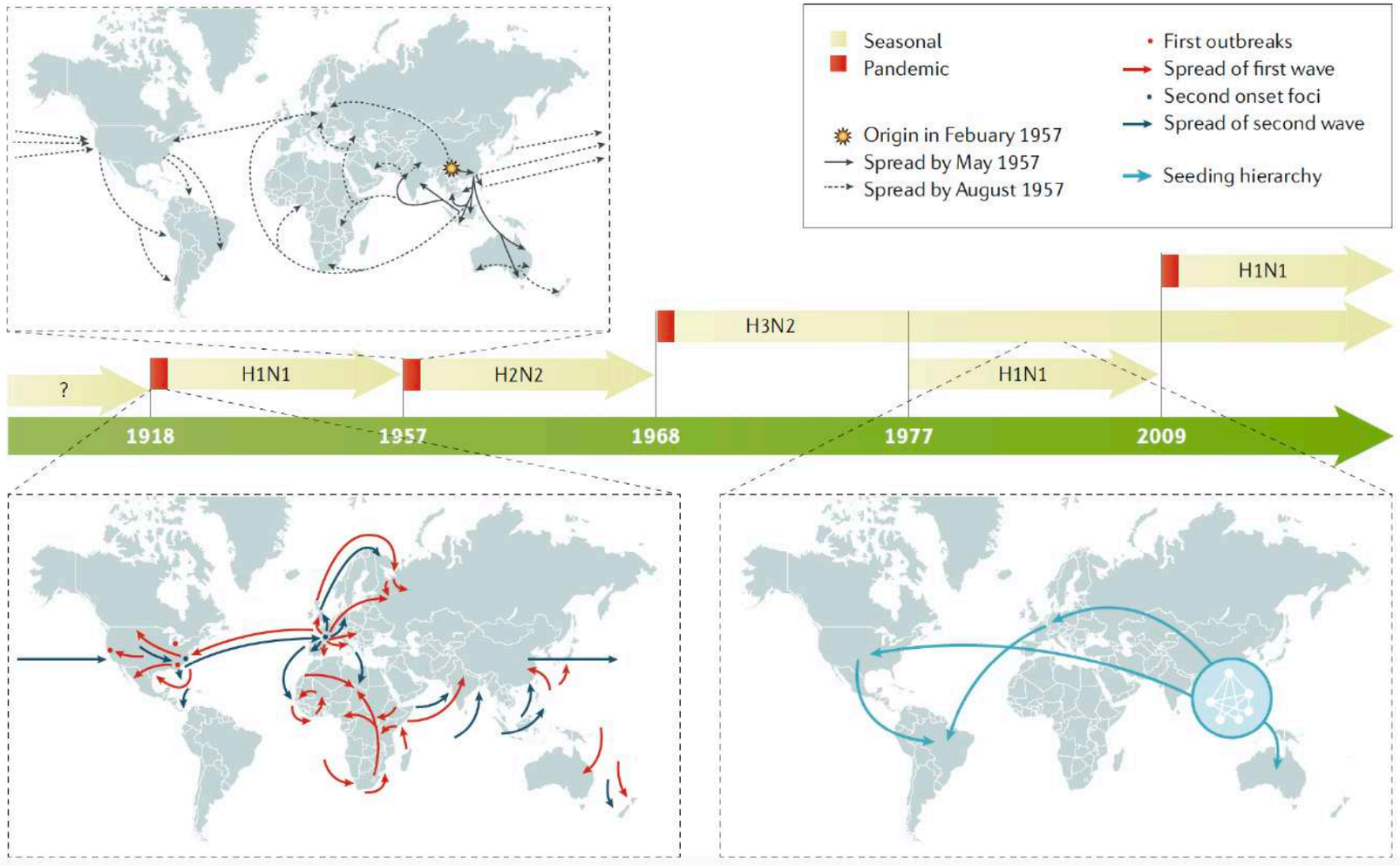
Madigan et al. 2020

Influenza Virus



- **Enveloped virus**
- **Negative-strand RNA viruses** are complementary in base sequence to the mRNA that is formed
- **Segmented genome (13.5 kb)**
- **8 linear single-stranded molecules ranging 890 to 2341 nucleotides**
- **Influenza virus exhibits antigenic shift in which segments of the RNA genome from two different viral strains infecting the same cell are reasorted**

Madigan et al. 2020



Kramer et al., 2018

Influenza viruses are capable of evading the antibody mediated immunity induced during previous infections or vaccinations by gradually accumulating mutations in HA and NA

Each influenza virus isolate receives a unique name according to a set of rules.

First, the name denotes the type of influenza virus (A, B, C or D), followed by the host species from which the virus was isolated (if not specified, the isolate is considered human), the geographical location at which the virus was isolated, the isolate number and the year of isolation.

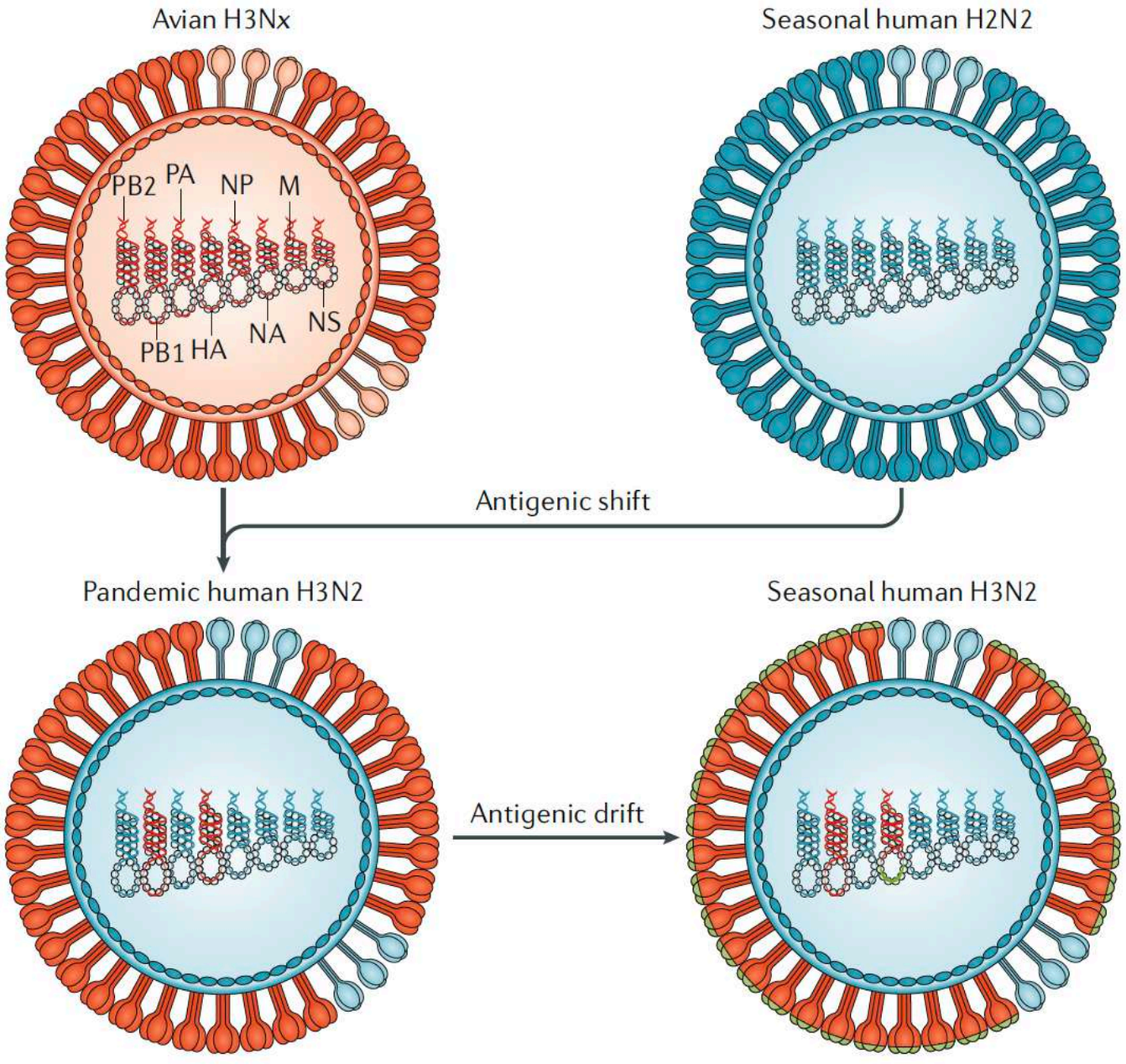
In the case of influenza A viruses, the haemagglutinin (HA) and neuraminidase (NA) subtype is also usually indicated after the viral isolate name.

For example, influenza A/Turkey/Ontario/6118/1968 (H8N4) virus is an influenza A virus isolated from a turkey in Ontario in 1968, isolate number 6118; the virus isolate has an HA from the HA antigenic subtype 8 and an NA from the NA antigenic subtype 4.

Kramer et al., 201[illegible]8

Genome rearrangement in human hosts

In poultry, the viral strains are transmitted both by aerosol and faecal contamination and cause systemic haemorrhagic disease and death



Kramer et al., 2018

- **Antigenic shift is thought to trigger major outbreaks of influenza because immunity to the new forms of the virus is essentially absent from the population**
- **Reassortment generates hybrid influenza virions that express unique surface proteins unrecognized by the immune system**
- **Once the virus becomes established in humans, the virus begins to drift, as is the case with all other human seasonal influenza viruses.**
- **During drift, small antigenic changes in the HA protein generated by mutation are selected to increase immune evasion, although not as dramatically as during shift**

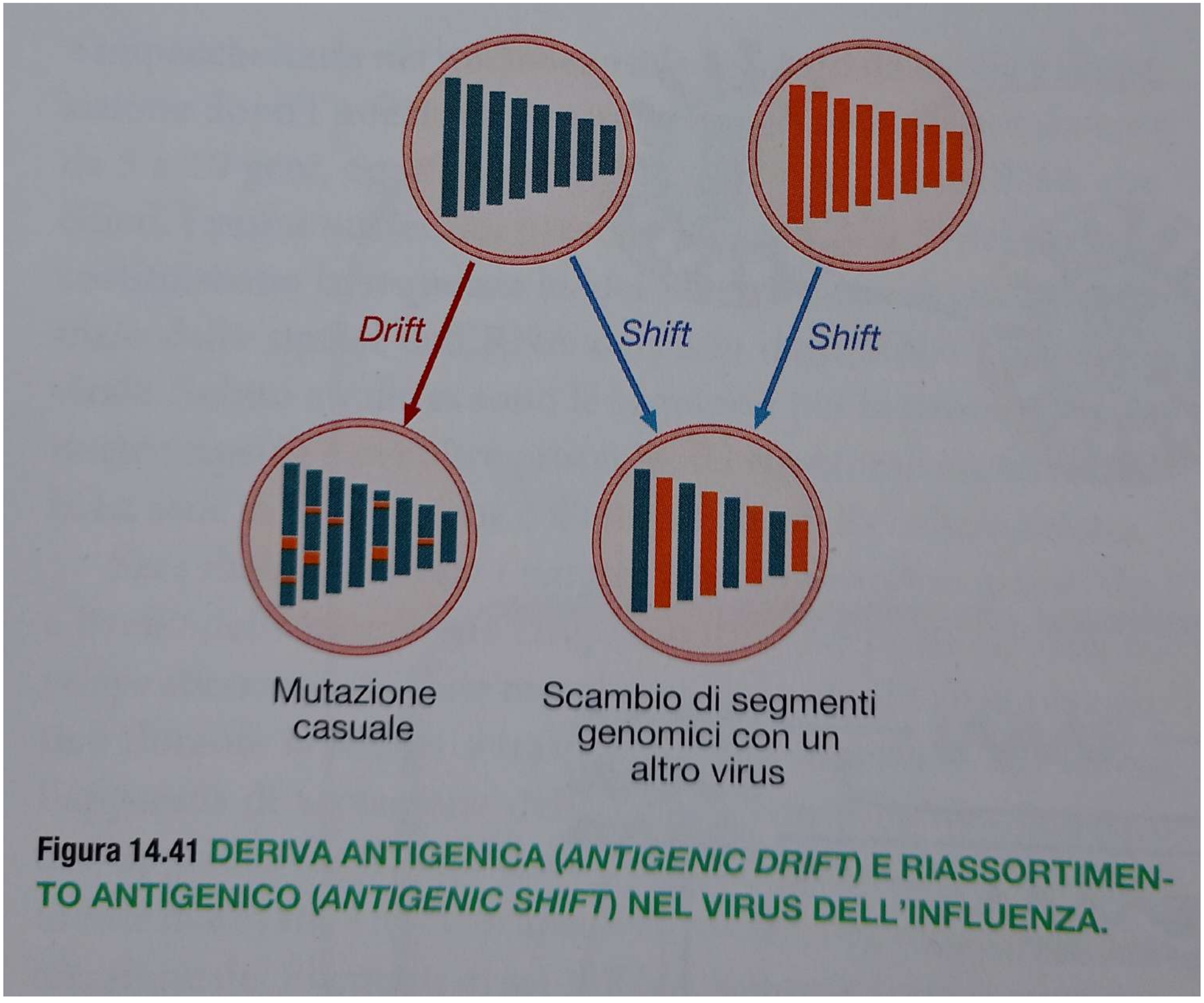
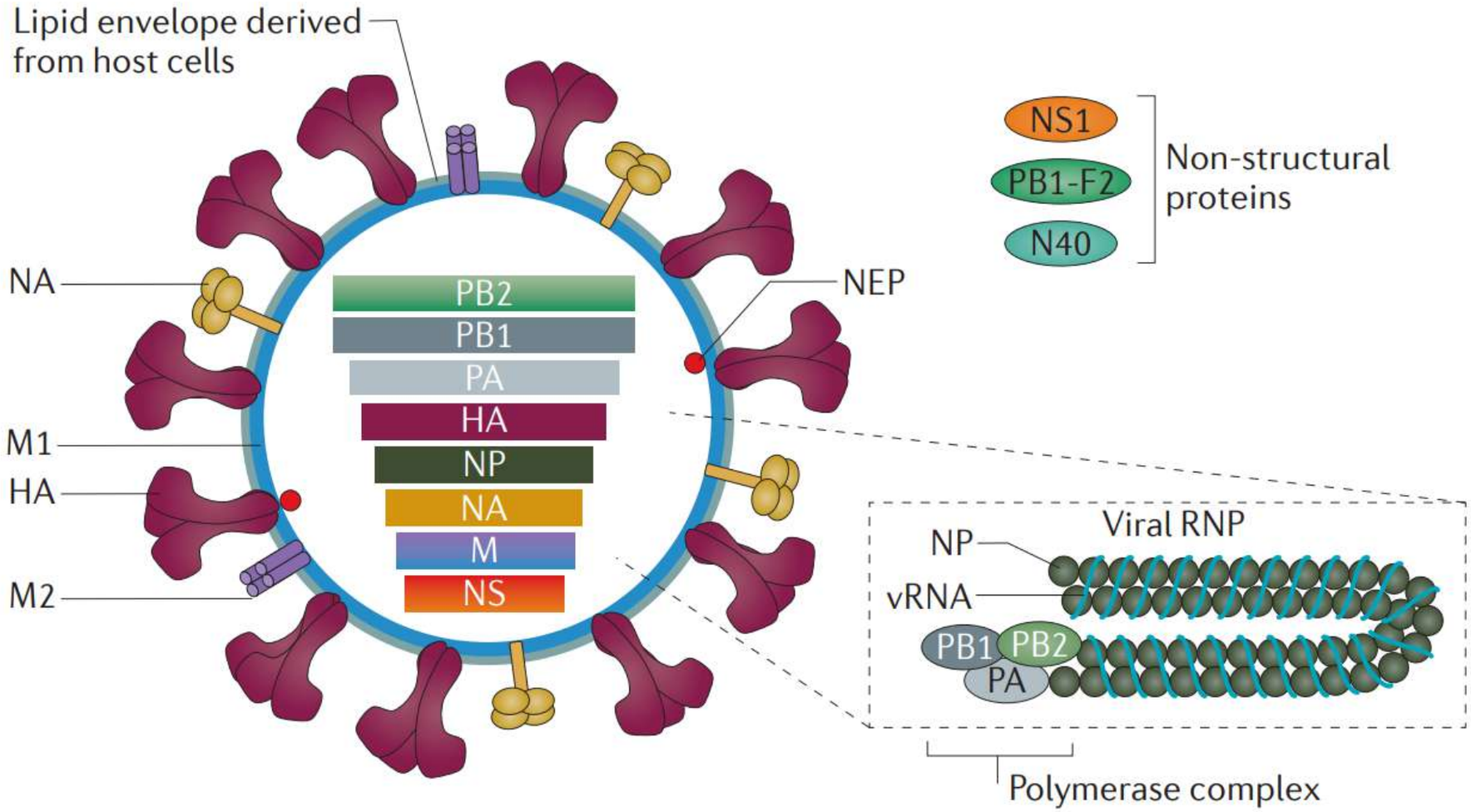


Figura 14.41 DERIVA ANTIGENICA (*ANTIGENIC DRIFT*) E RIASSORTIMENTO ANTIGENICO (*ANTIGENIC SHIFT*) NEL VIRUS DELL'INFLUENZA.

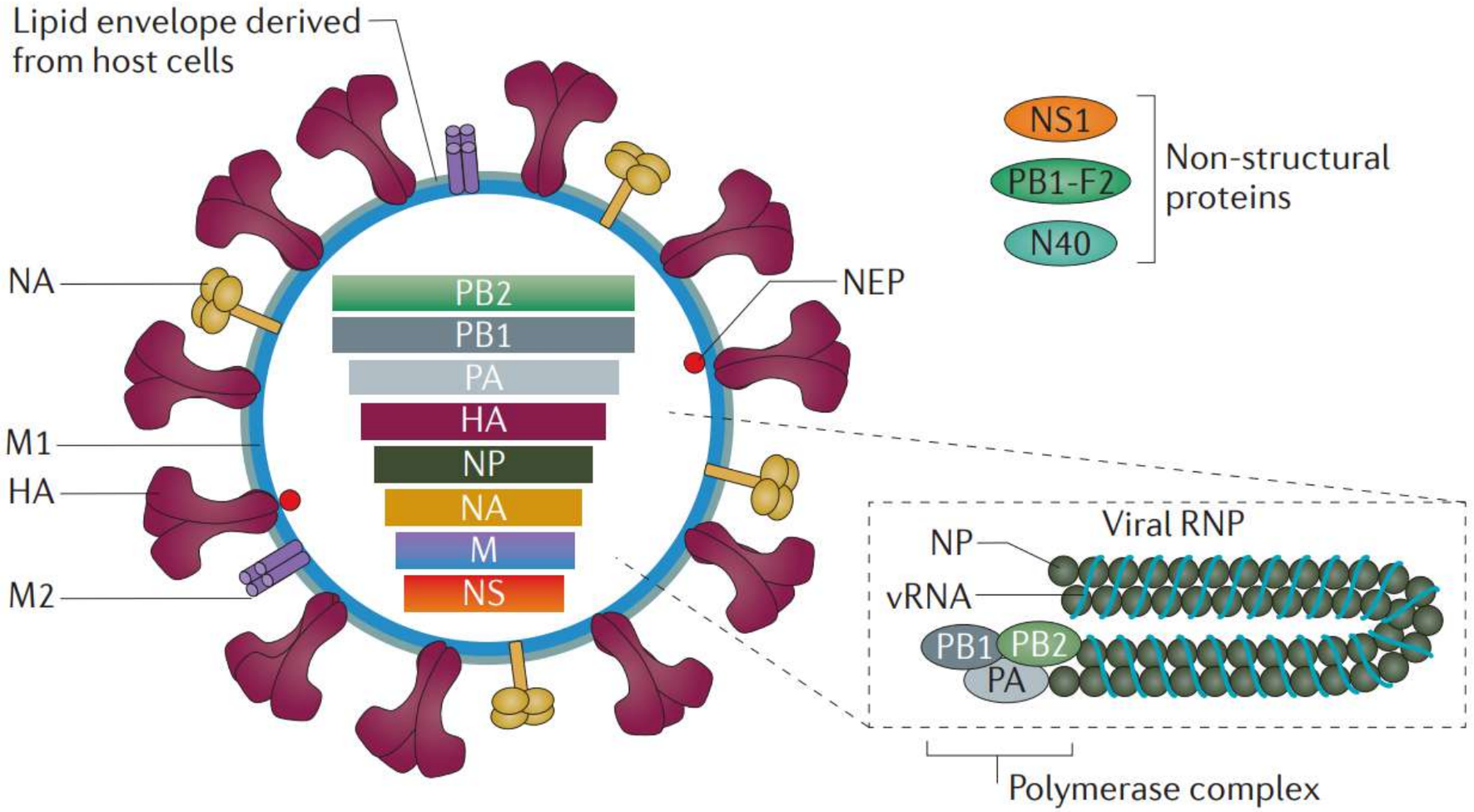
8 segment genome, I



Medina & García-Sastre, 2011

- **NS segment encodes nuclear export protein (NEP) & host antiviral response antagonist non-structural protein 1 (NS1)**
- **M segment encodes matrix protein M1 & the ion channel M2**
- **HA segment the receptor-binding protein haemagglutinin (HA)**

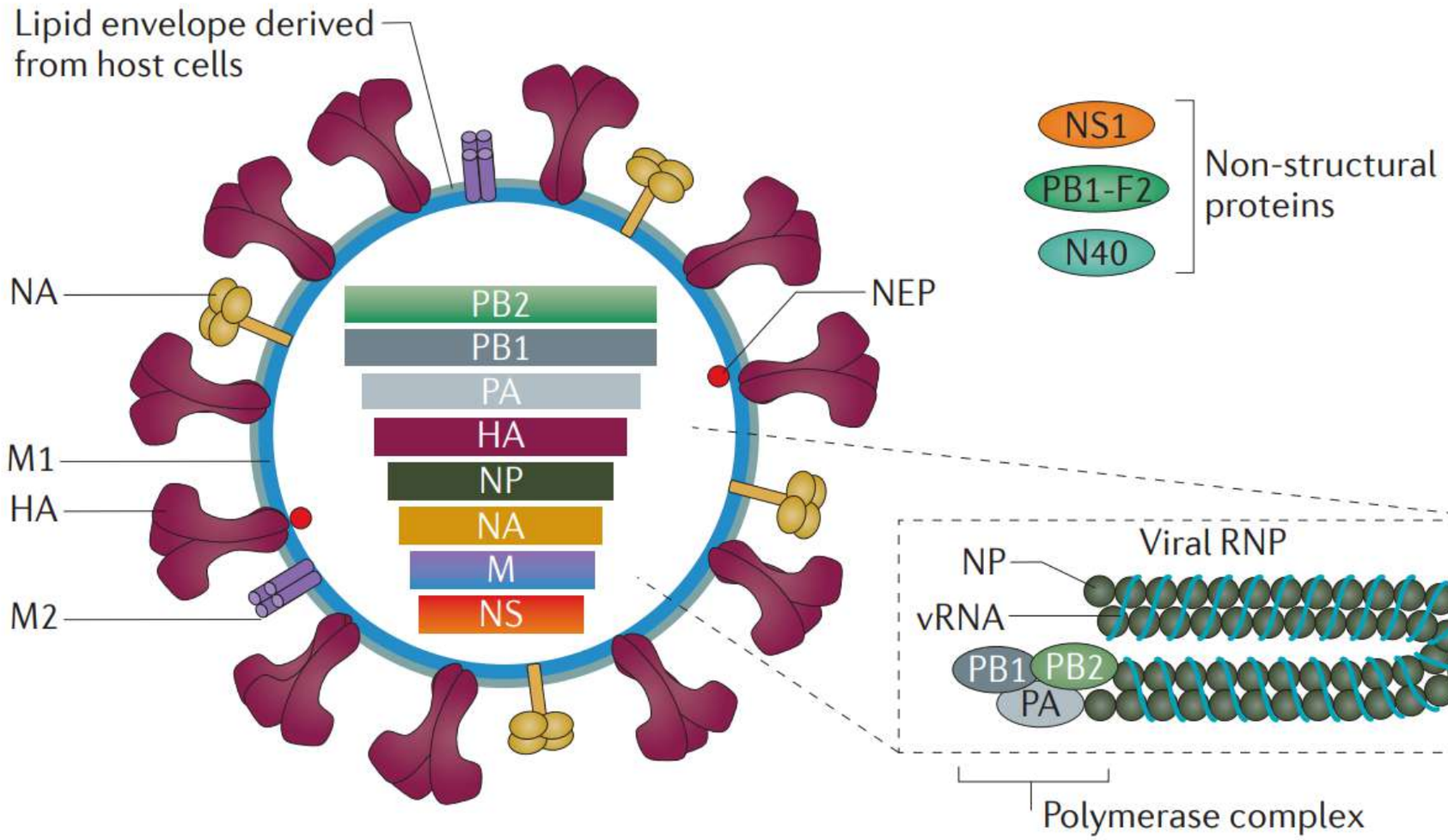
8 segment genome, II



Medina & García-Sastre, 2011

- **NA segment the silica acid-destroying enzyme neuraminidase (NA)**
- **NP segment nucleoprotein (NP)**
- **RNA-dependent RNA polymerase complex from PB1, PB2 and PA segments**

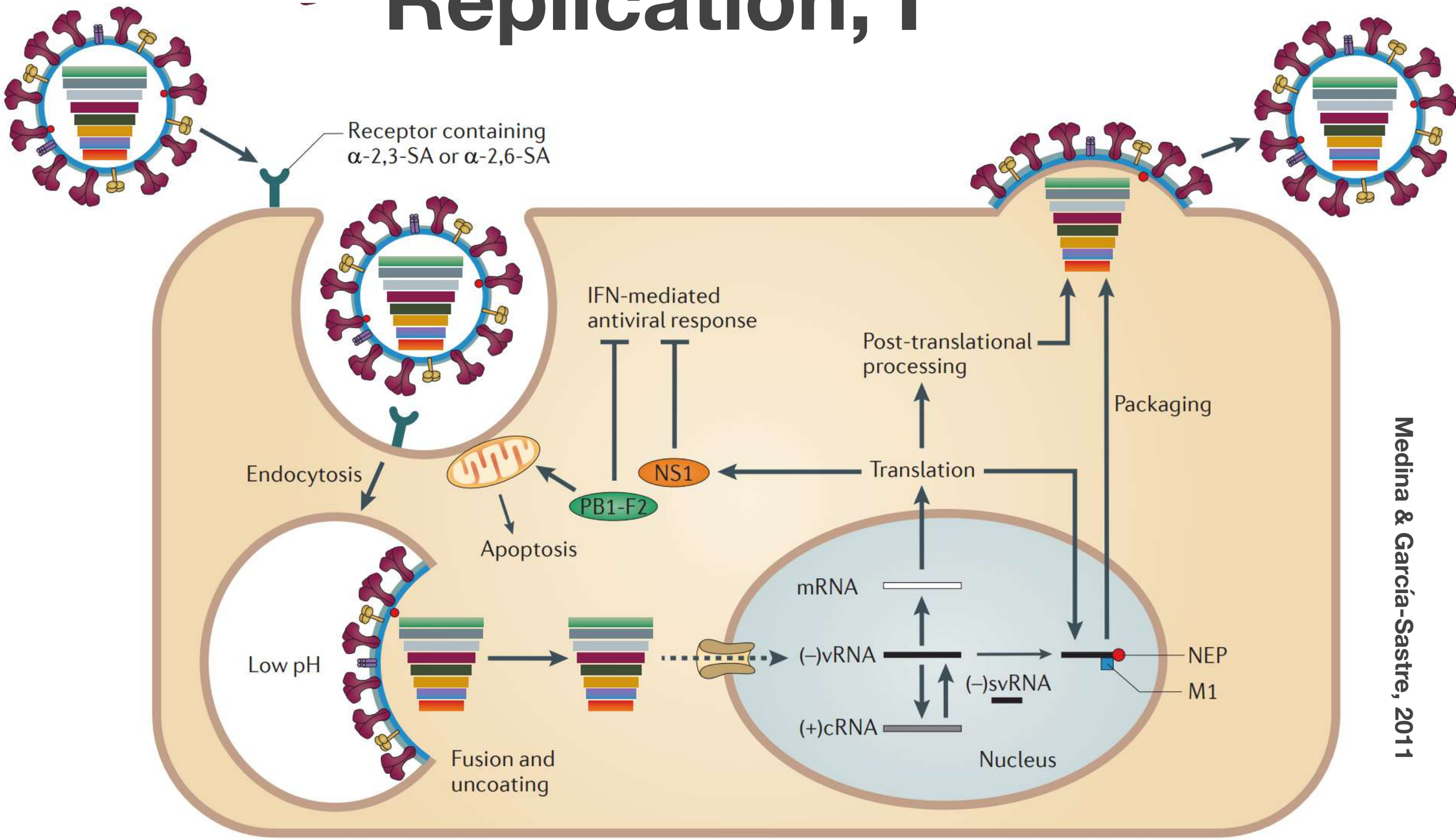
8 segment genome, III



Medina & García-Sastre, 2011

Within the virion, *each of the eight viral segments forms a viral ribonucleoprotein (RNP) complex*: **viral RNA is wrapped around NP, and this structure is then bound to the viral polymerase complex**

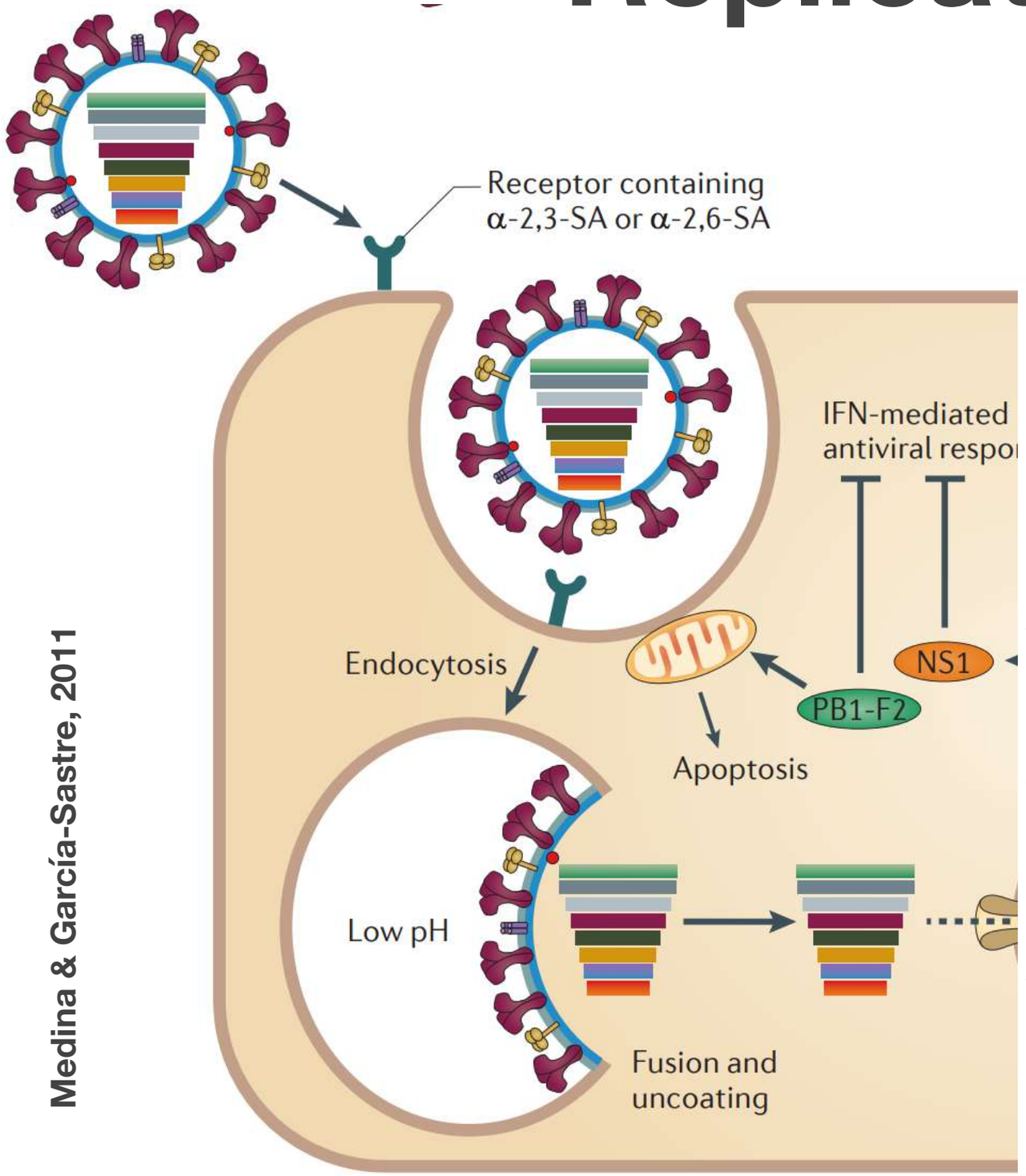
Replication, I



Medina & García-Sastre, 2011

Virus enters the cell by receptor-mediated endocytosis

Replication, II



HA cleavage by cellular proteases is required to expose HA peptide that is responsible for fusion between viral envelope and endosomal membrane

Acidification of endocytic vesicle opens M2 ion channel, resulting in acidification of the inside of virion, a process that is required for proper uncoating of RNP complexes that contain viral genome

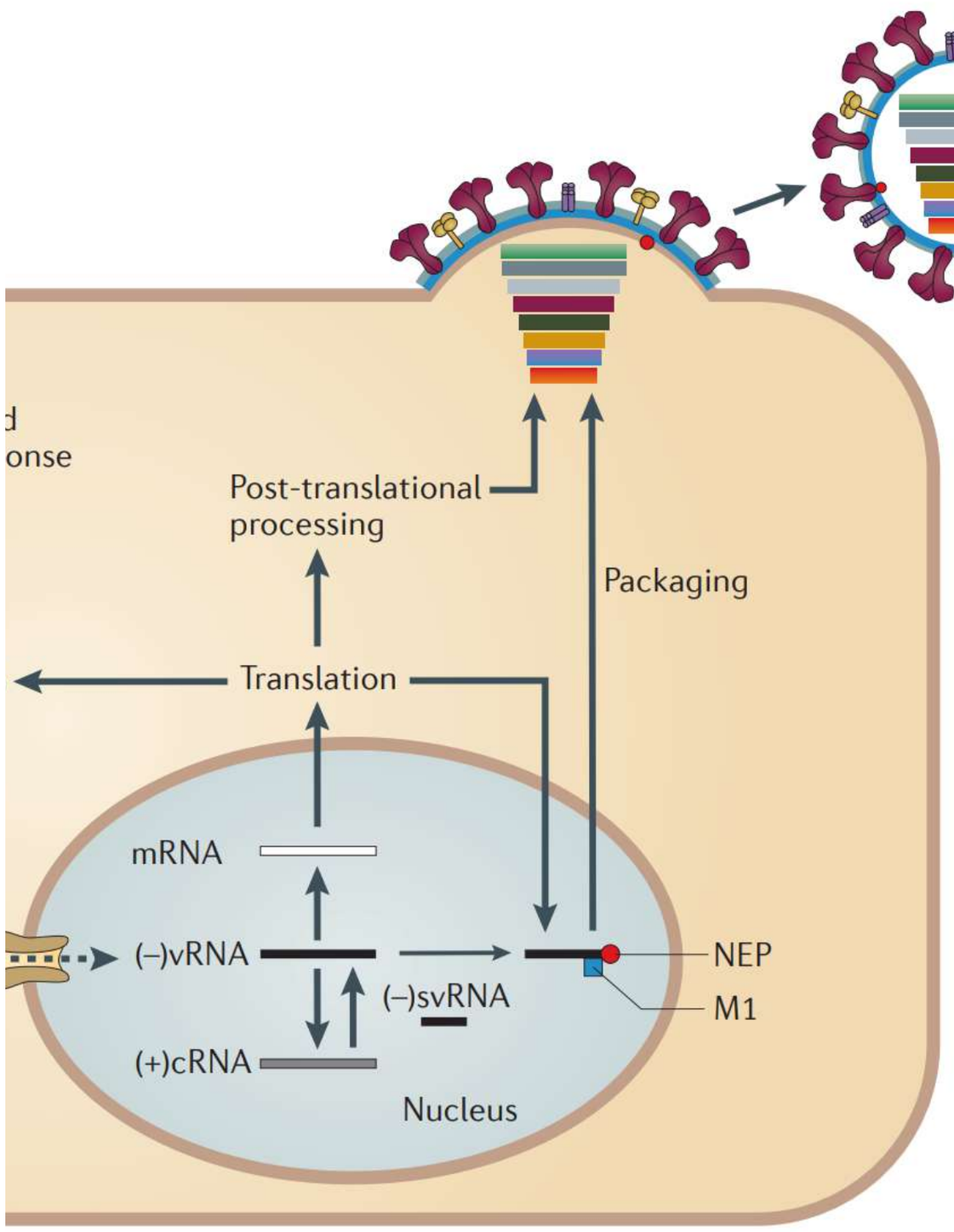
Acidification of endosome also triggers pH-dependent fusion step that is mediated by HA and results in cytoplasmic release of RNP complexes

Medina & García-Sastre, 2011

Replication, III

RNA-dependent RNA polymerase transcribes and replicates negative-sense viral RNA ((–) vRNA), giving rise to three types of RNA molecules:

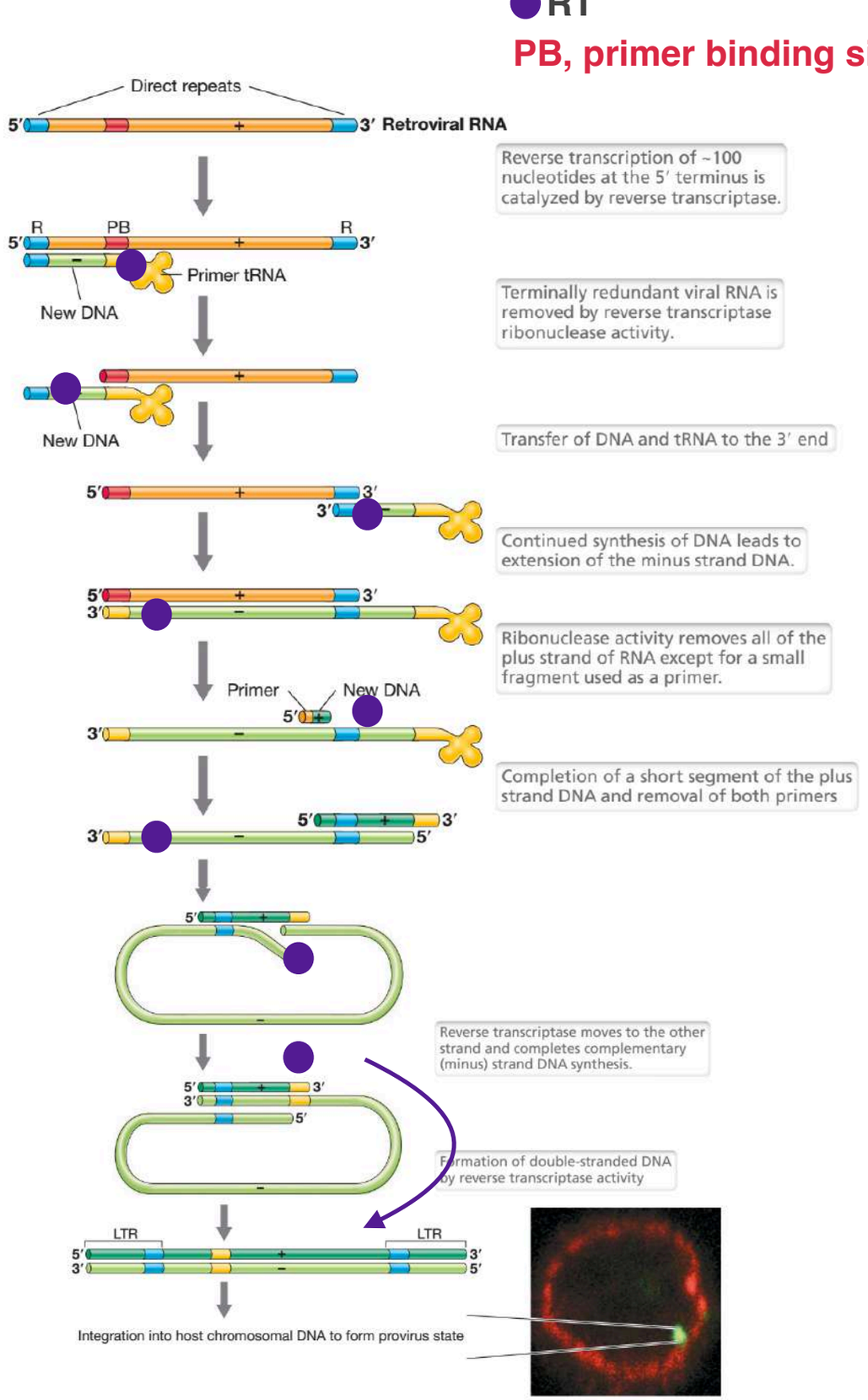
1. **Complementary positive-sense RNA ((+)cRNA), which it uses as a template to generate more vRNA**
2. **Negative-sense small viral RNAs (svRNAs), which are thought to regulate switch from transcription to replication**
3. **Viral mRNAs, which are exported to cytoplasm for translation**



Medina & García-Sastre, 2011

Retrovirus, I

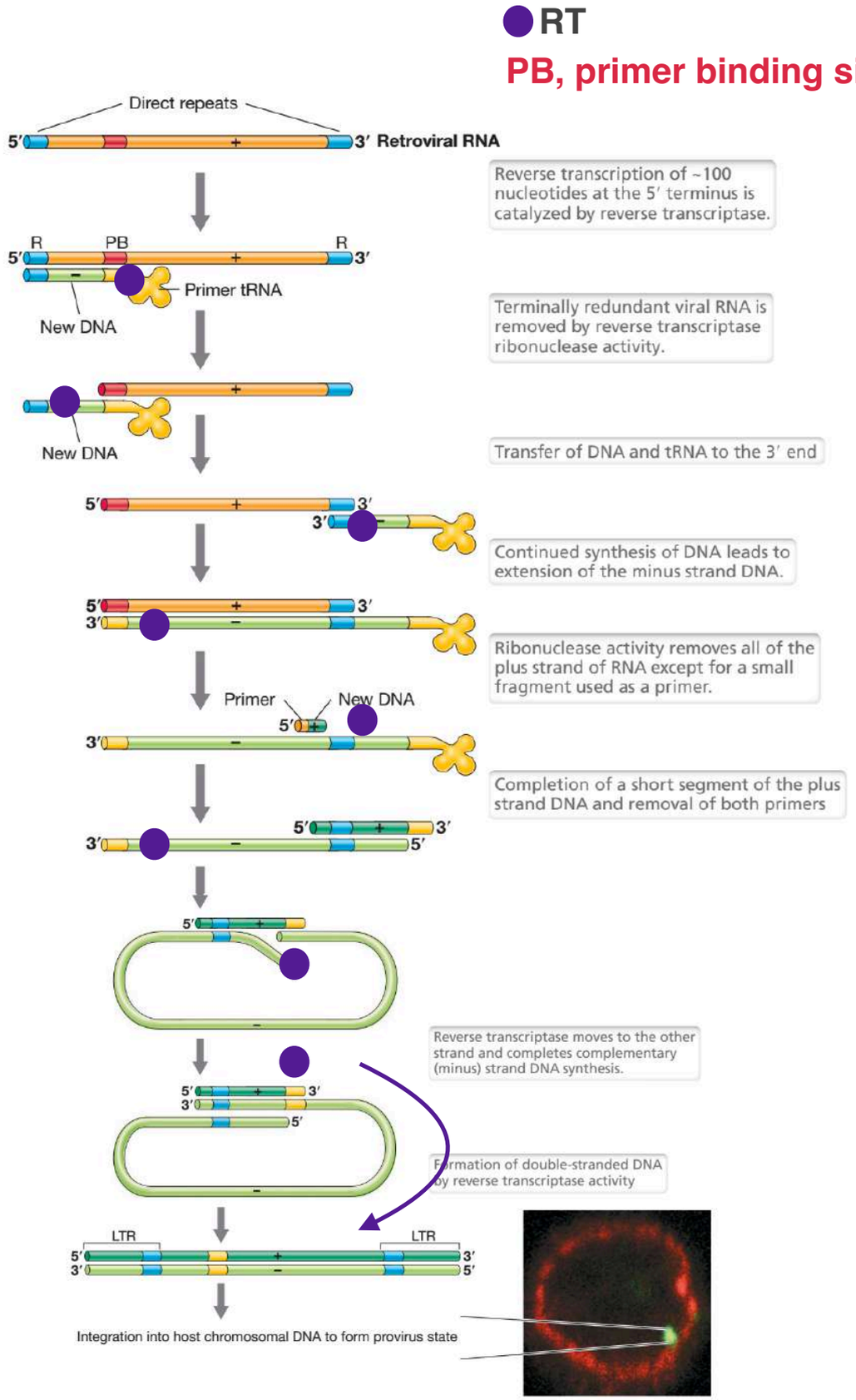
- ssRNA genomes (+)
- **Reverse transcriptase (RT)** has 3 enzymatic activities:
  1. **Reverse transcription** (to synthesize DNA from an RNA template), **3'—>5'**
  2. **Ribonuclease activity** (to degrade RNA strand of an RNA:DNA hybrid)
  3. **DNA polymerase** (to make double-stranded DNA from single-stranded DNA)
- **RT** needs a **primer for DNA** synthesis: **the viral tRNA**



Madigan et al. 2018

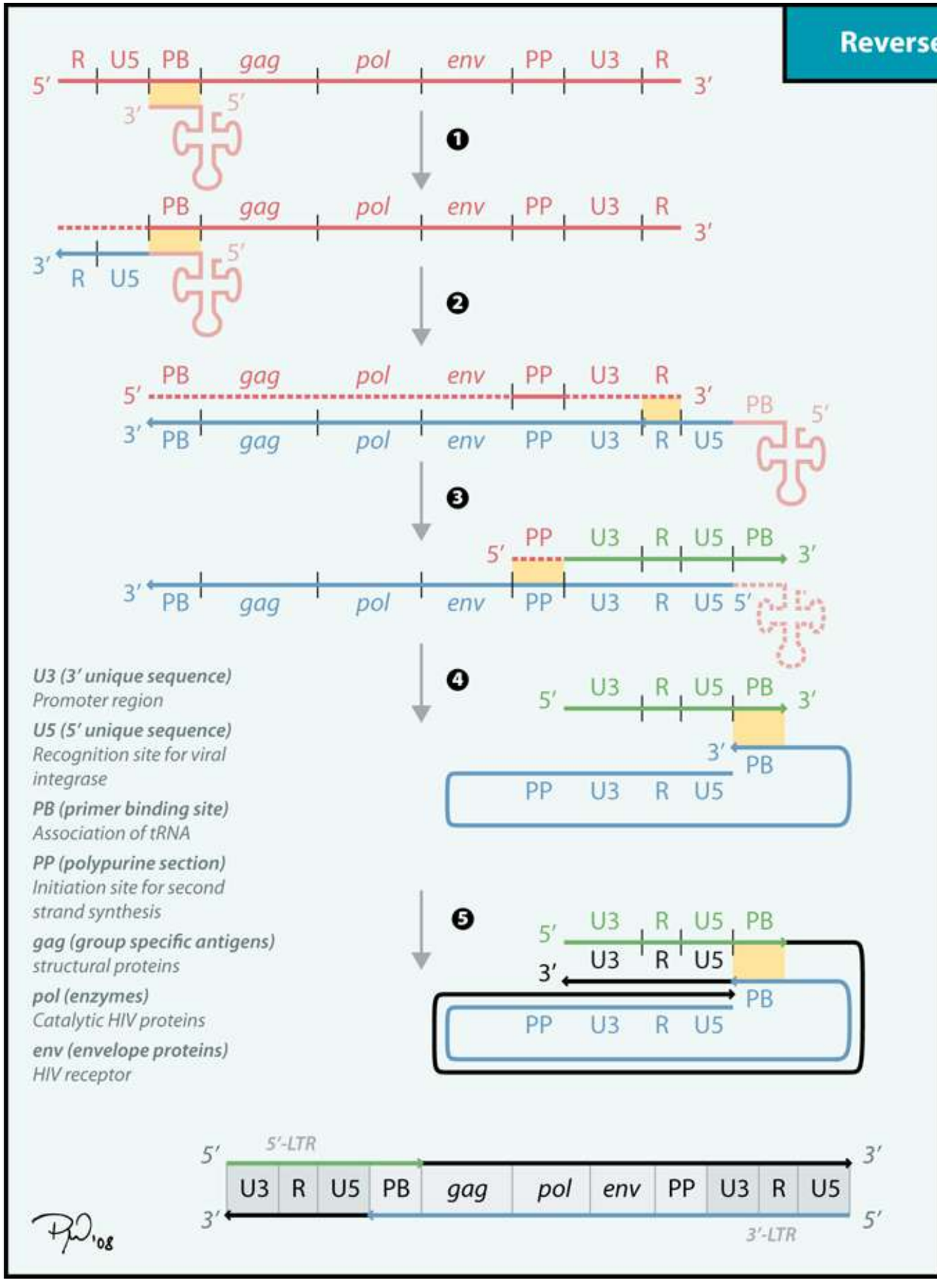
Retrovirus, II

- Using this primer, nucleotides near the 5′ terminus of RNA are reverse-transcribed into DNA
- Once reverse transcription reaches 5′ end of RNA, process stops
- Terminally redundant RNA sequences at 5′ end are removed by RT
- Formation of a small, ssDNA complementary to RNA segment at 3’ of viral RNA
- This short, ssDNA hybridizes with the other end of viral RNA molecule, where synthesis of DNA begins once again



Madigan et al. 2018

Reverse transcription of HIV-RNA into dsDNA



1 During transport to the nucleus, the viral ssRNA genome (red) is reverse transcribed into double strand DNA by the viral RT. Reverse transcription takes always place in 3′→5′ direction. The tRNA (rose), which hybridizes to the PB site, provides a hydroxyl-group for initiation of reverse transcription.
While a ssDNA (blue) sequence is synthesized, the complementary ssRNA is degraded by the RNase H function of RT.

2 The DNA-tRNA hybrid molecule is then transferred to the 3′-end of the template and is used for first strand synthesis. Afterwards, the ssRNA is degraded exept for the PP site, which serves as a new primer.

3 The initial second strand synthesis of ssDNA (green) starts from the 3′-end of PP, which will be finally degraded. The tRNA makes it possible to synthesize the complementary PB site.

4 After the tRNA is degraded, the first and second DNA strand hybridize at their PB sites, which they harbor on their ends.

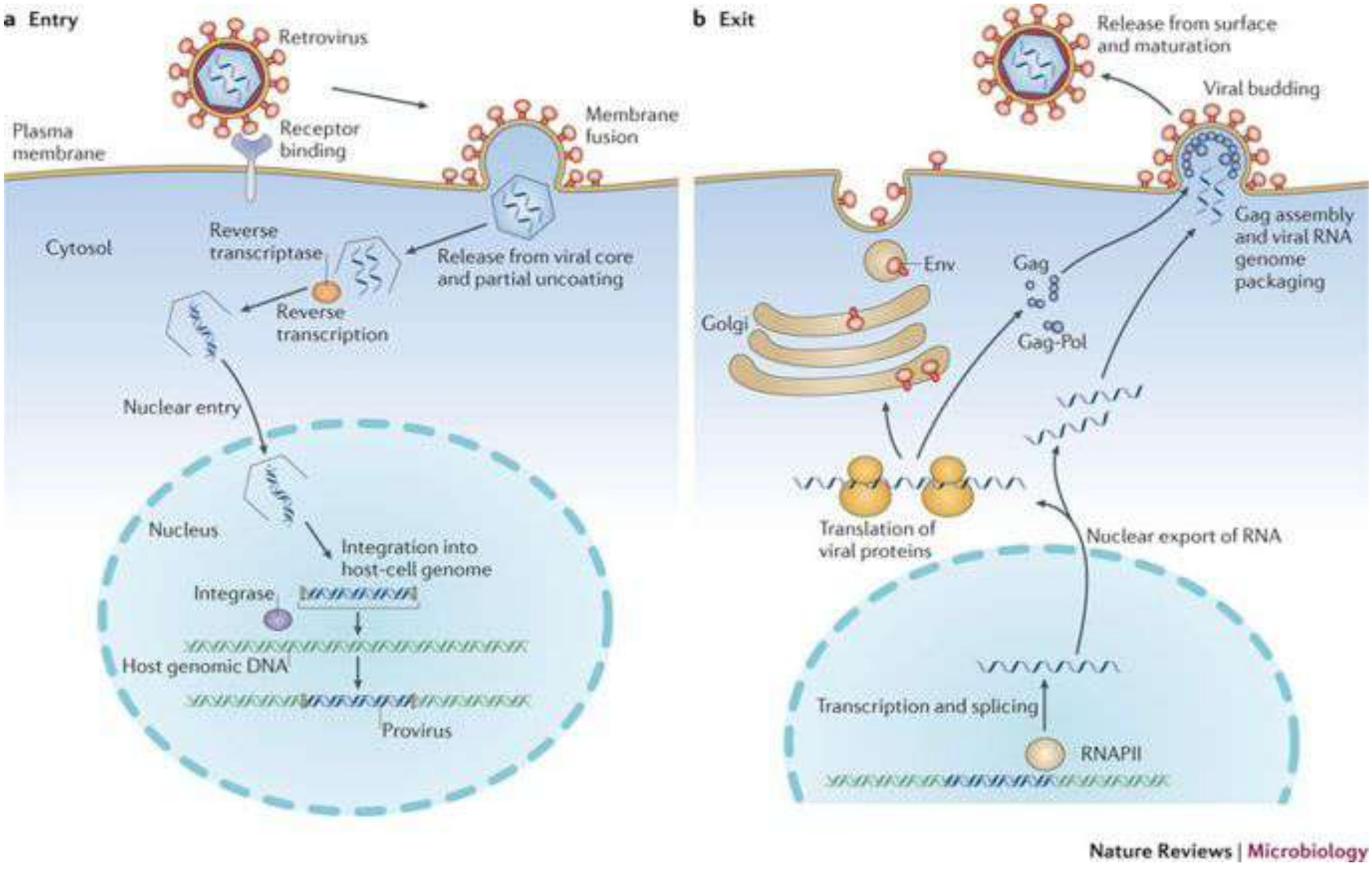
5 Both strands will be completed by the DNAP function of RT. Compared to the ssRNA, both dsDNA ends now have a U3–R–U5 sequence that is also called long terminal repeat (LTR).

Colors: RNA (red), transfer RNA (rose), first DNA strand (blue), second DNA strand (green), DNA completions (black), site with complementarity (yellow; not shown for all sequences).

RNase H: Ribonuclease H; **tRNA**: transfer RNA; **ssDNA**: single strand DNA; **ssRNA**: single strand RNA; **dsDNA:** double strand DNA; **RT:** Reverse transcriptase; **DNAP**: DNA polymerase.

Not drawn to scale! Enzymatic reactions, interacting proteins, splicing sites, and binding site ψ are omitted for clarity.
In style of *Mudrow S, Falke D, Truyen U (2003). Molekulare Virologie, 2. Aufl. (engl.: Molecular Virology, 2nd ed.) Spekt Akad Verl. Heidelberg, Berlin.*

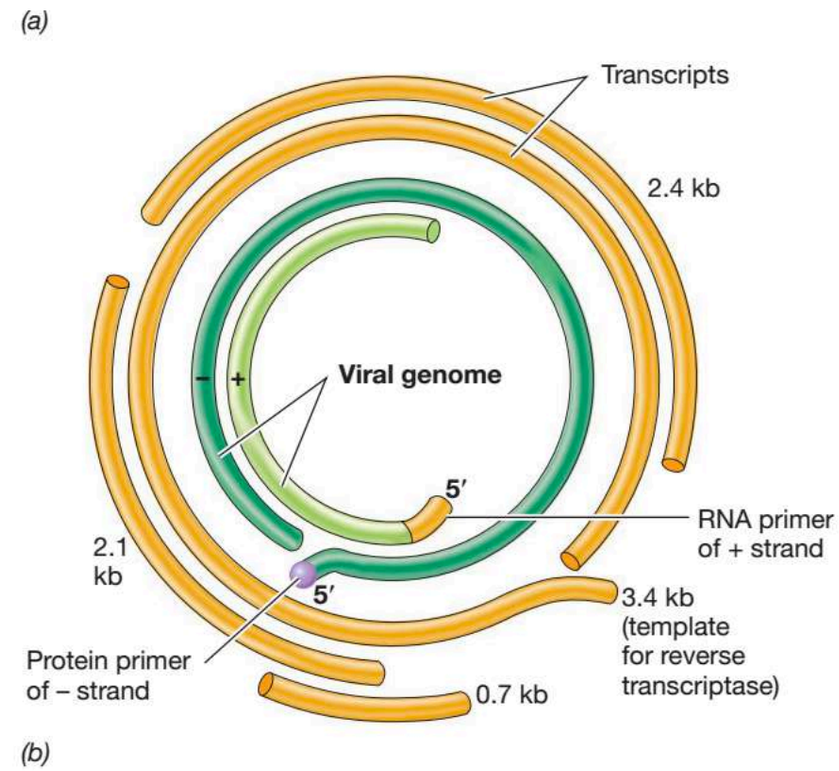
Retrovirus



Stoye, 2012

Hepadnavirus, I

- Hepatitis B, HBV
- **Partially ds DNA**
- 3-4 kb pairs genome
- Hepadnavirus genomes encode several proteins by employing **overlapping genes**
- Hepadnaviral **reverse transcriptase (RT) functions as a protein primer for synthesis of one DNA strand**
- **DNA genome is replicated via an RNA intermediate**

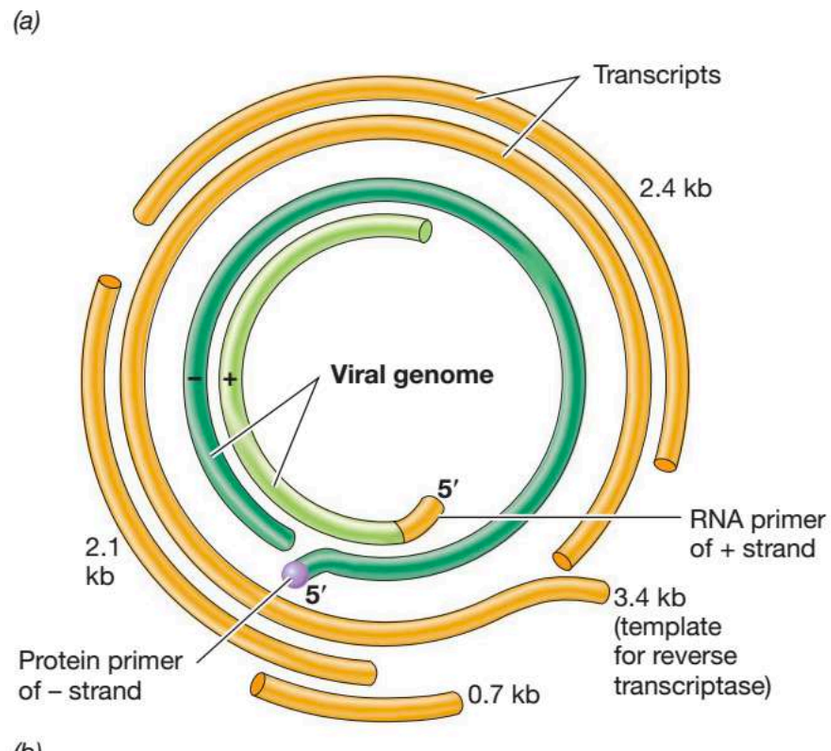


- *In retroviruses, the RNA genome is replicated through a DNA intermediate*

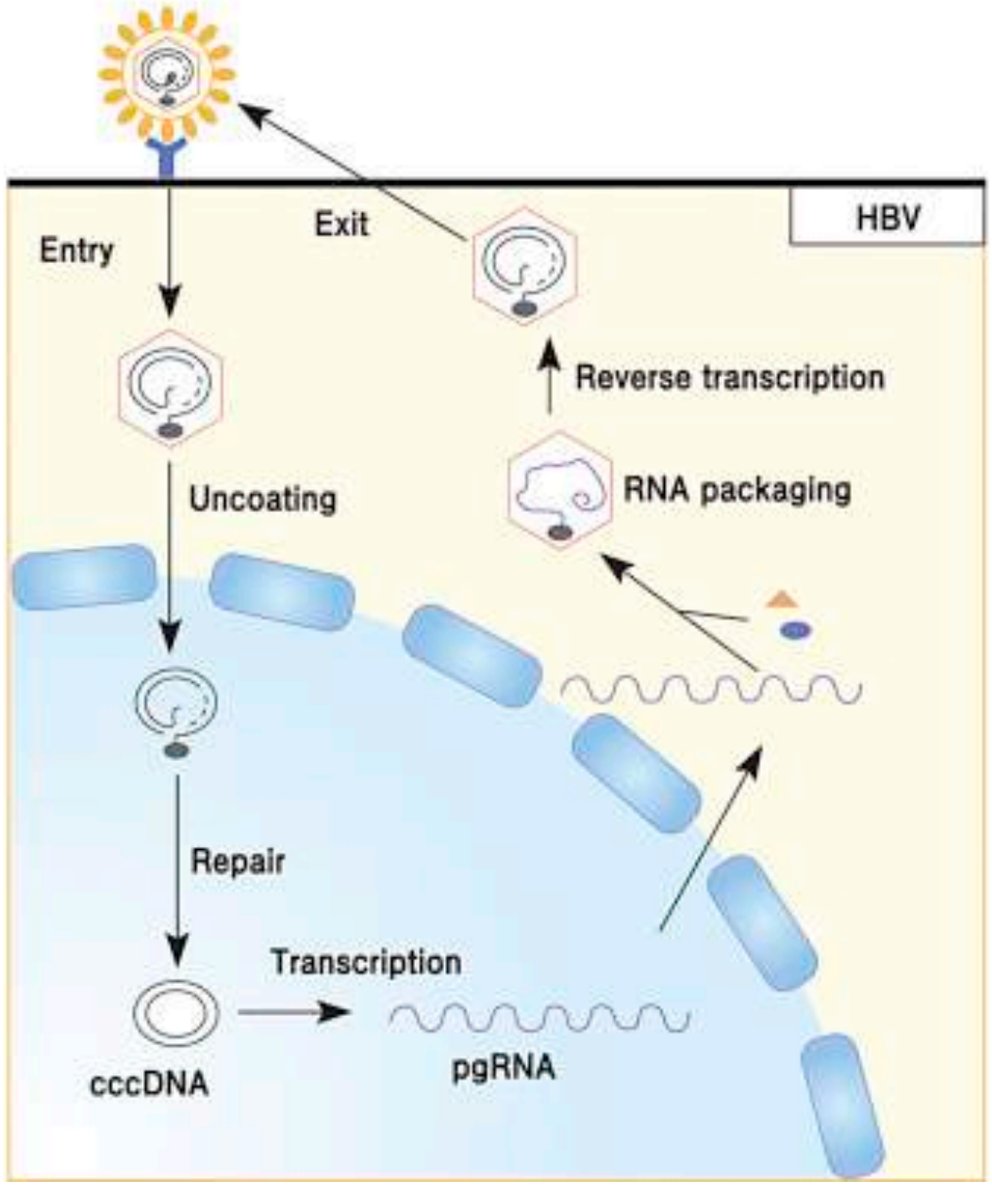
Madigan et al. 2018

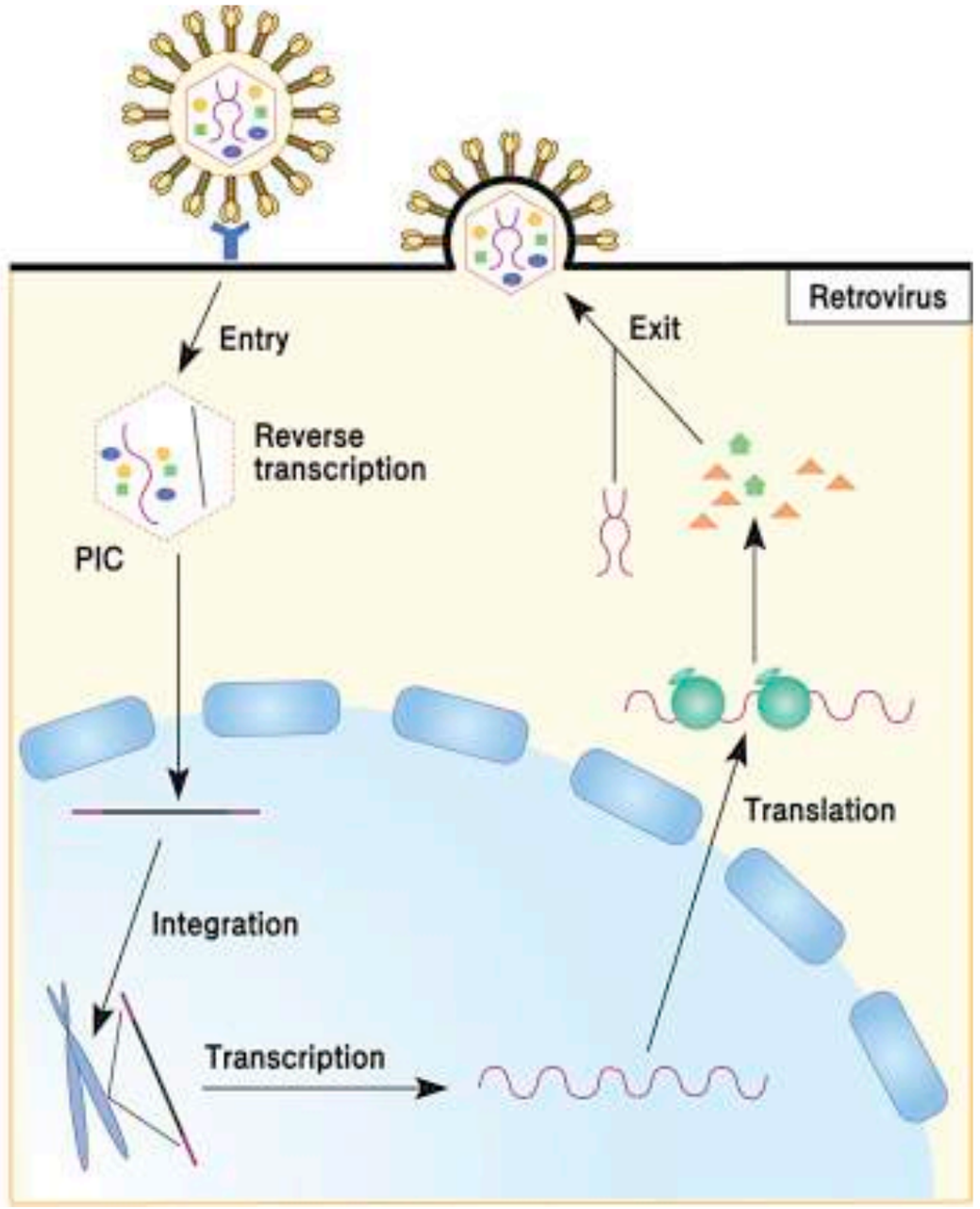
Hepadnavirus, II

- Nucleocapsid enters host nucleus
- Partial genomic DNA strand is completed by **viral polymerase to form an entire dsDNA**
- **Transcription by host RNA polymerase** yields **four size classes** of viral **mRNAs** translated to proteins
- The **largest** of these transcripts is > the viral genome and, with RT, associates with viral proteins in host cytoplasm to form genomes for new virions
- RT forms single-stranded DNA off of this large transcript inside virion to form the (-)strand of DNA genome and then uses this as a template to form a portion of (+) strand, —> partially ds genome



Madigan et al. 2018





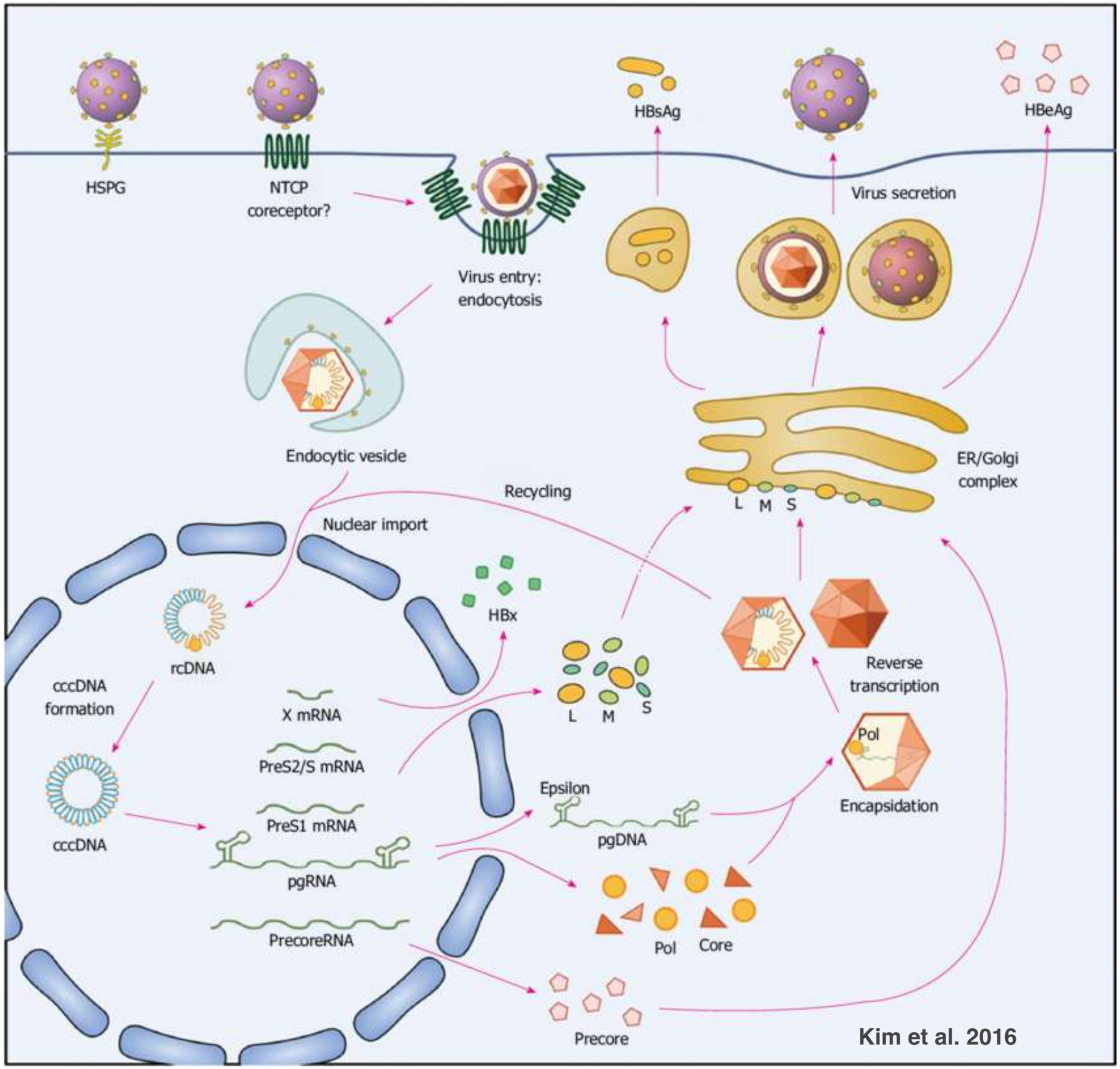
Wang-Shick, 2017

- Both retrovirus and HBV replicate via reverse transcription,RT
- A **retrovirus has an RNA molecule** inside the virion particles, whereas **HBV has a DNA molecule**
- The step during the virus life cycle at which the reverse transcription step occurs is different
- The **retroviral capsids exit the cells without reverse transcription, RT during viral entry**
- **HBV capsids exit the cell following viral reverse transcription**

Sophisticated changes in viron informative architecture

- Relaxed circular DNA genome, not complete
- Covalently closed circular DNA (cccDNA)
- Reverse transcription of a pregenomic RNA (pgRNA) in core particles leading to synthesis of the relaxed circular DNA (rcDNA)
- cccDNA, the template for viral RNA transcription

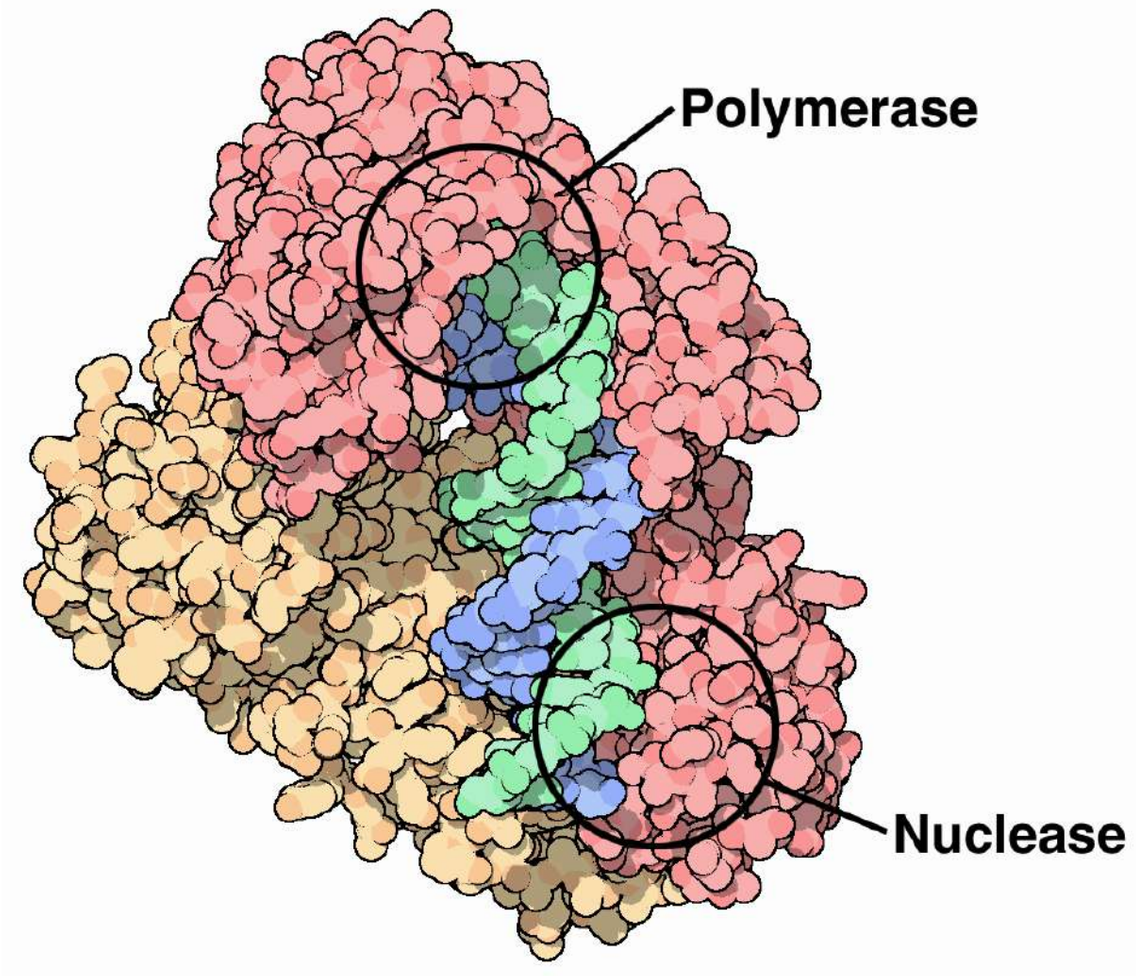
Hu & Seeger, 2015



Reverse transcriptase (RT)

- In 1970 Temin, Mizutan, and Baltimore, working independently, reported the discovery of an **enzyme that could synthesize proviral DNA <**
  — RNA viral genome

- In 1975 Temin, Baltimore, and Dulbecco (who mentored both Temin and Baltimore) were awarded the Nobel Prize for Physiology or Medicine “for their discoveries concerning the interaction between tumour viruses and the genetic material of the cell

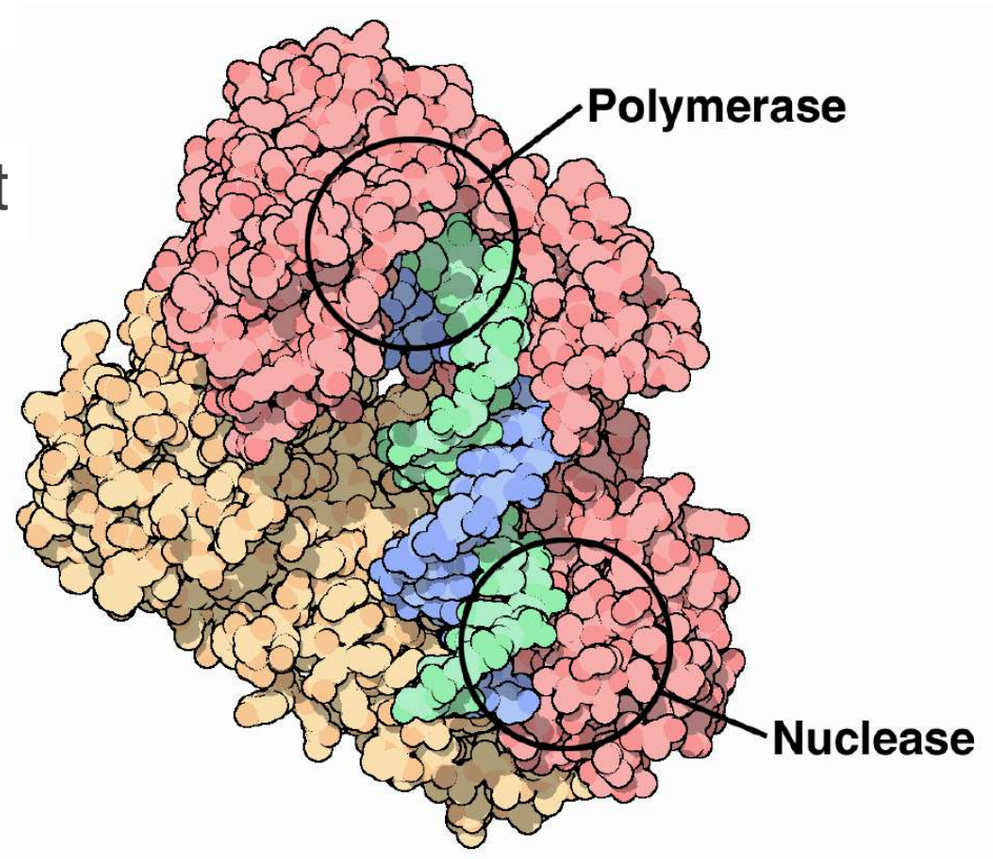


https://pdb101.rcsb.org/motm/33

Reverse transcriptase (RT)

Retroviruses have ssRNA genomes (+)
Hepadnaviruses have dsDNA genomes

- **RT is composed of 2 different subunits, encoded by the same gene with diverse 3D arrangement**
- After the protein is made, one of the subunits is clipped to a smaller size (yellow) so that it can form the proper mate with one full-sized subunit (red)
- **RT makes lots of mistakes, up to about one in every 2,000 bases that it copies**
- **The errors allow HIV to mutate rapidly**, finding drug resistant strains in a matter of weeks after treatment begins

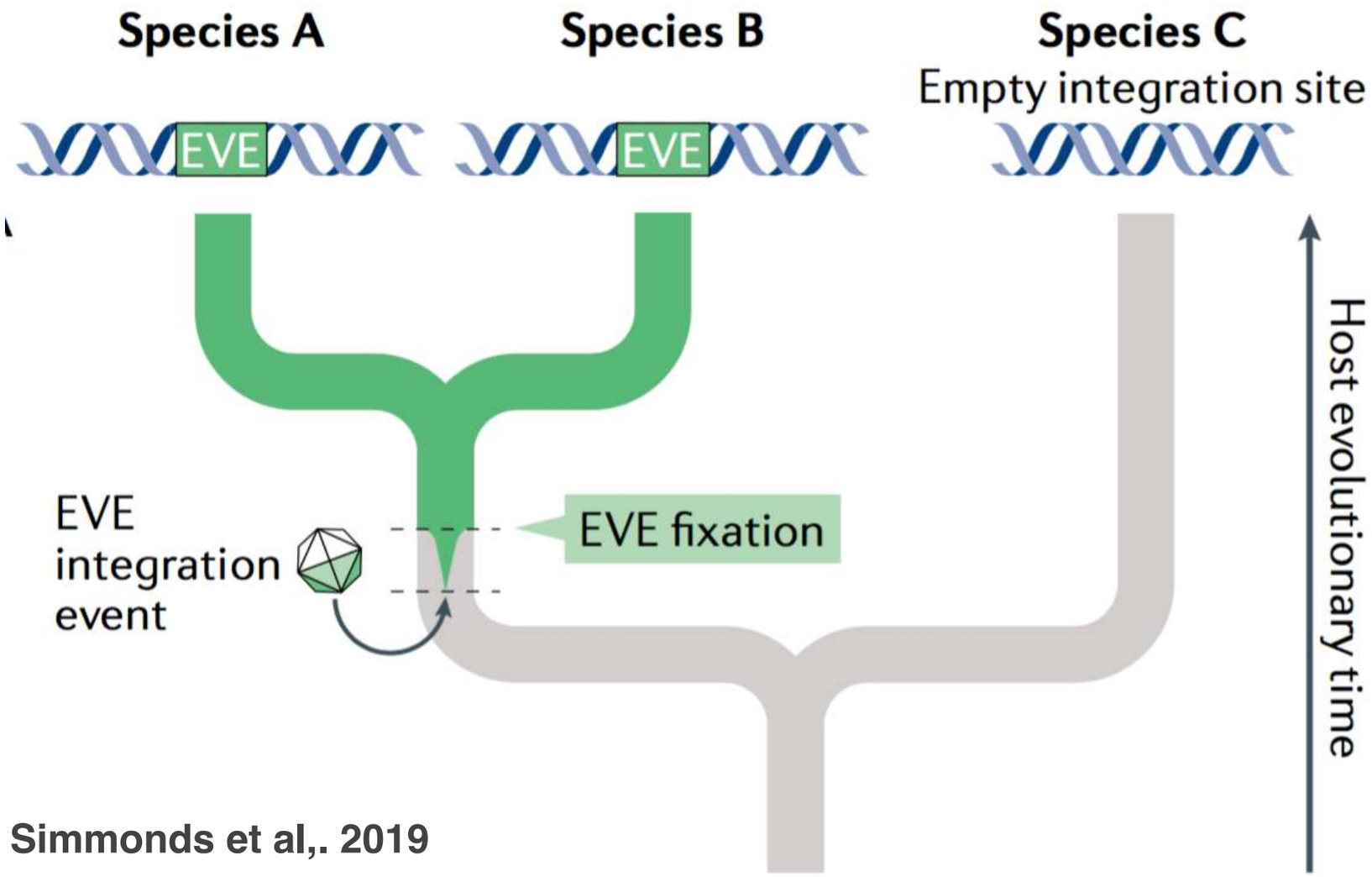


https://pdb101.rcsb.org/motm/33

Endogenous retroviruses

- The **presence of viruses was positively selected** because they promoted cellular variation and functional diversification
- **Endogenous retroviruses (ERVs), which are ancient traces of past infections** found as viral footprints in the genome of different species
- About 8% of the human genome is made of endogenous retroviral-like elements
- These viral footprints are virus-associated sequences that closely **resemble present-day retroviral** (e.g., HIV) elements, including the 5’ and 3’ long terminal repeats (LTR), and the coding genes gag, pro-pol, and env
- Long-time persistence in the host genome —> accumulation of **mutations** as well as insertions and deletions, which have generally **affected their capacity to produce infectious virions**

Endogenous viral elements



Simmonds et al,. 2019

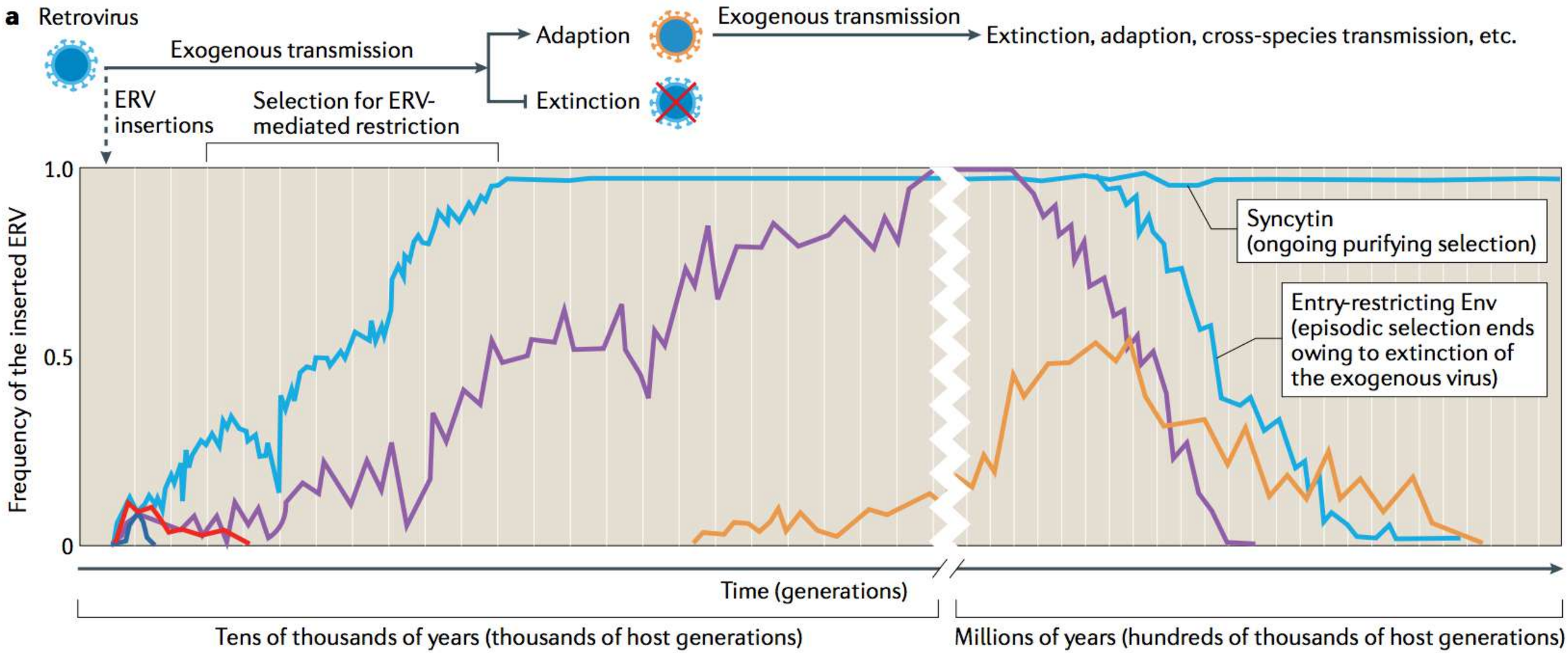
Endogenous lentiviruses in rabbits integrated over 12 million years (Myr)

Similaparvoviruses (>30 Myr), circoviruses (>60 Myr) and bornaviruses in elephants, hyraxes and tenrecs (>93 Myr)

Ebola-like virus that integrated over 30 Myr ago into the genomes of rodents

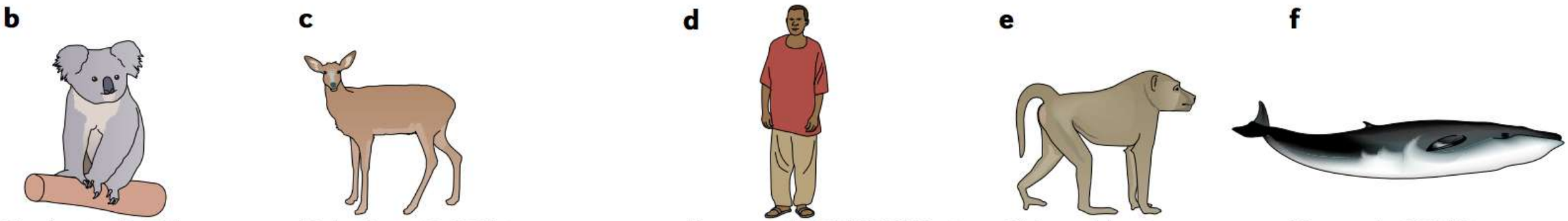
As part of host genomes, endogenous viral elements (EVEs) are inherited, vertically passing from parents to offspring to create a genomic fossil record stretching back millions of years

Hypothetical evolutionary stages of endogenous retrovirus (ERV) loci



Johnson, 2019

Examples of ERVs at different stages in the evolutionary process in natural populations



- Retroviruses have been infecting vertebrates for over 450 million years
- In retrovirus lifecycle is **retrotransposition**, in which the RNA-based virus genome is reverse transcribed and integrated into the DNA of the host cell
- Occasional integrations into the **germline genomes** of egg or sperm cells have the potential to become **endogenous retroviruses (ERVs)** that become fixtures in the host genome

Johnson, 2019

Endogenous retroviruses, II

- Present-day human endogenous retroviruses probably contribute to **pluripotency of human cells**, and **genome regulation and placenta fusion, brain development**

- ERVs: RNA transcribed from HERV-K provide stem cells in embryos **pluriplotency** but when expressed in adults —> cancers of the testes

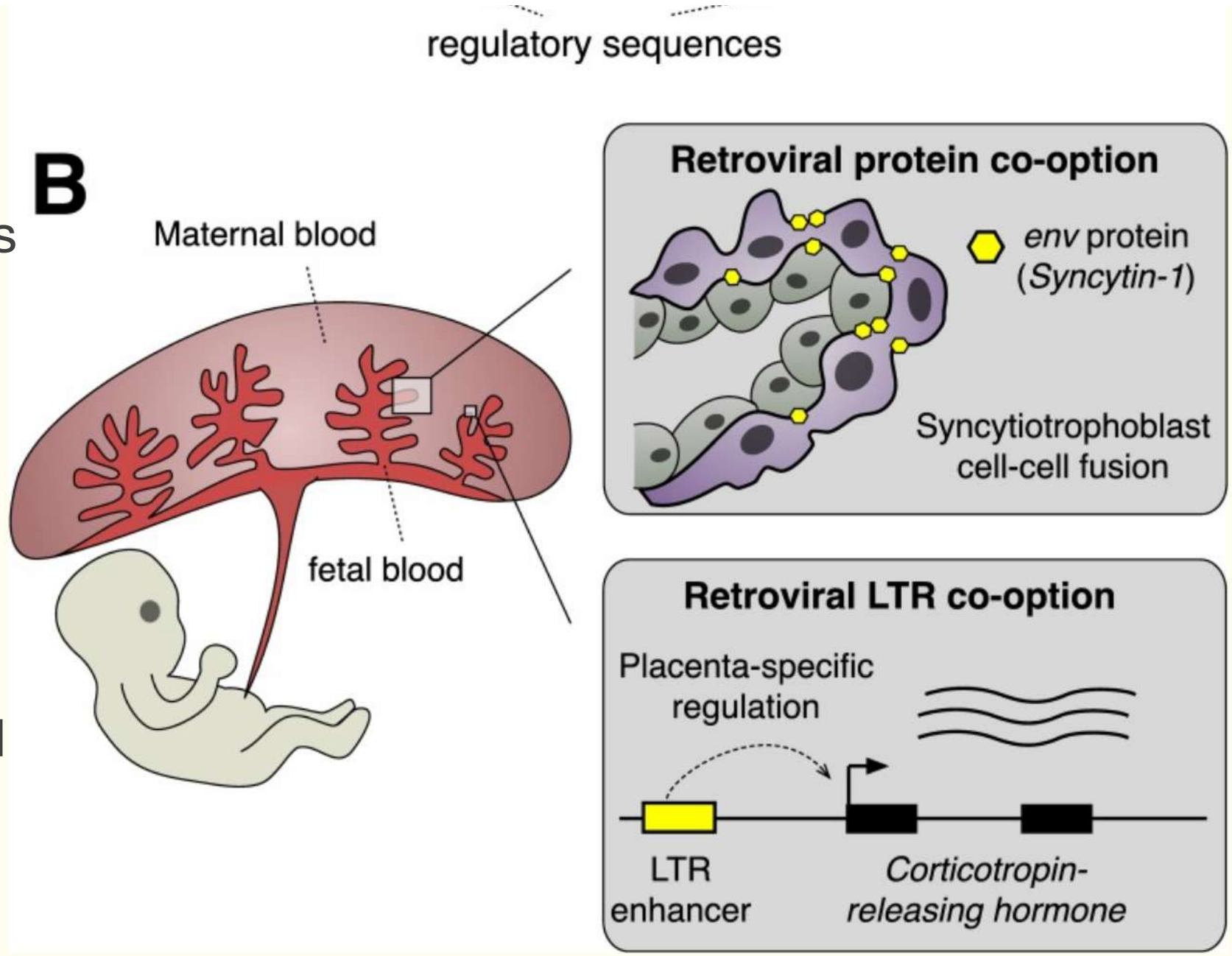
- LINE-1, has a viral origin 6000 letter DNA —> reversetranscriptase —-> 500K copies a grand total of **17% in human genome brain development in mouse brain embryo** —> are actively operate as retrotrasposons

- *ERVs can function as genomic regulators of transcription*
- *ERVs can trigger inflammation response*
- *ERVs are unregulated in some kind of cancer*

The placenta goes viral: Retroviruses control gene expression in pregnancy

ERVs—> genetic novelties —> 10 lineages in mammalians —> placenta cells are working together—> fusion for merging syncytin-1

The fusion of cells from the placenta is mediated by syncytin, a protein in HERV-W endogenous retroviruses



Mallet etl a.l., 2004; Chuong, 2018; Domingo, 2020

Functional properties of antiviral compounds

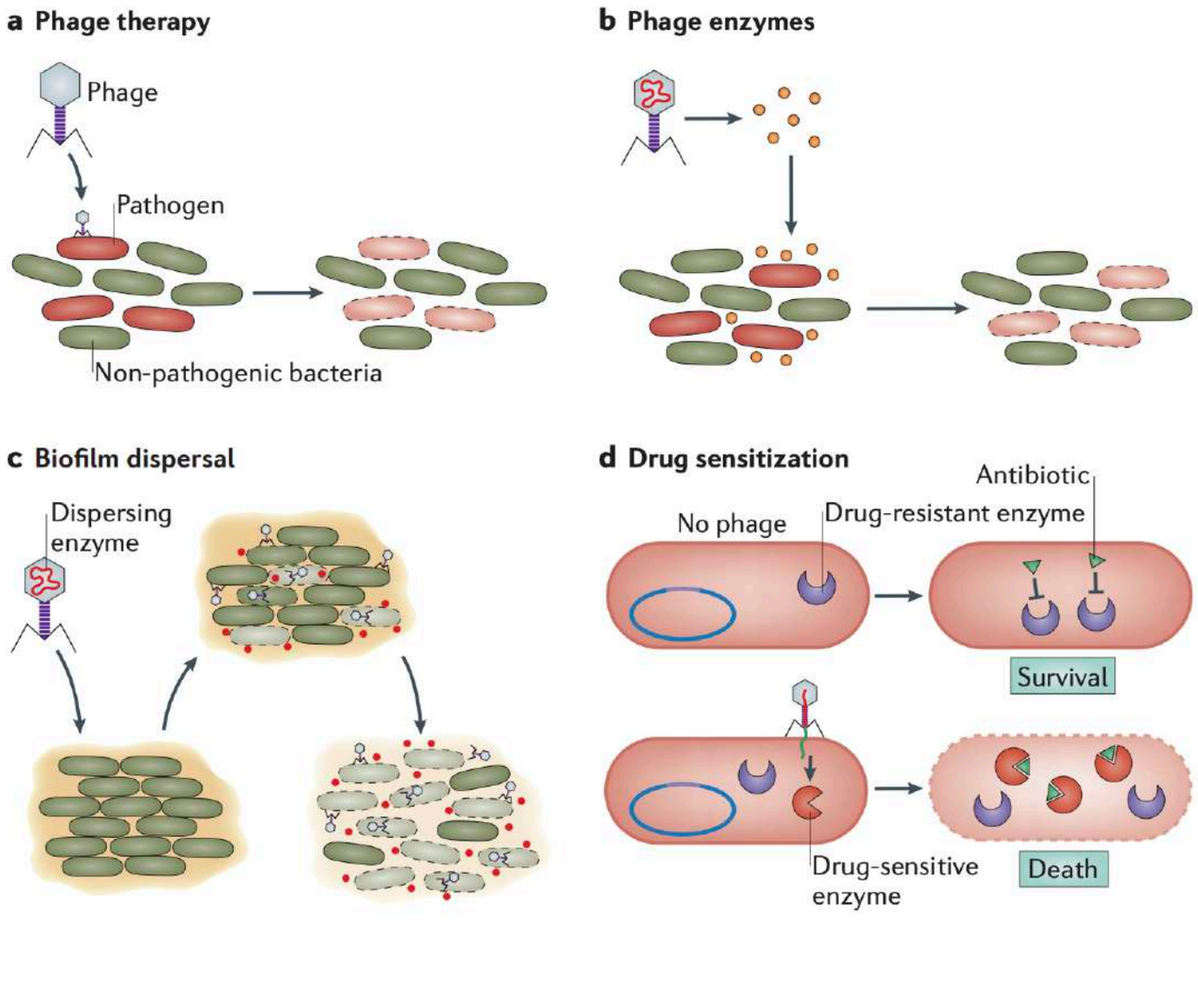
TABLE 28.6 Antiviral compounds

Examples	*Mechanism of action*	*Virus affected*
Enfuvirtide	Blocks fusion of HIV with T lymphocyte membrane	HIV (human immunodeficiency virus)
α, β, γ-Interferon	Induces proteins that inhibit viral replication	Broad spectrum (host-specific)
Oseltamivir (Tamiflu®) and zanamivir (Relenza®)	Block active site of influenza neuraminidase	Influenza A and B
Nevirapine	Reverse transcriptase inhibitor	HIV
Acyclovir (Figure 30.42)	Viral polymerase inhibitor	Herpes viruses, *Varicella zoster*
Zidovudine (AZT) (Figure 30.48*a*)	Reverse transcriptase inhibitor	HIV
Ribavirin	Blocks capping of viral RNA	Respiratory syncytial virus, influenza A and B, Lassa fever
Cidofovir	Viral polymerase inhibitor	Cytomegalovirus, herpesviruses
Tenofovir (TDF)	Reverse transcriptase inhibitor	HIV
Indinavir, saquinavir (Figure 28.35)	Viral protease inhibitors	HIV

Madigan et al. 2020

Phage therapy

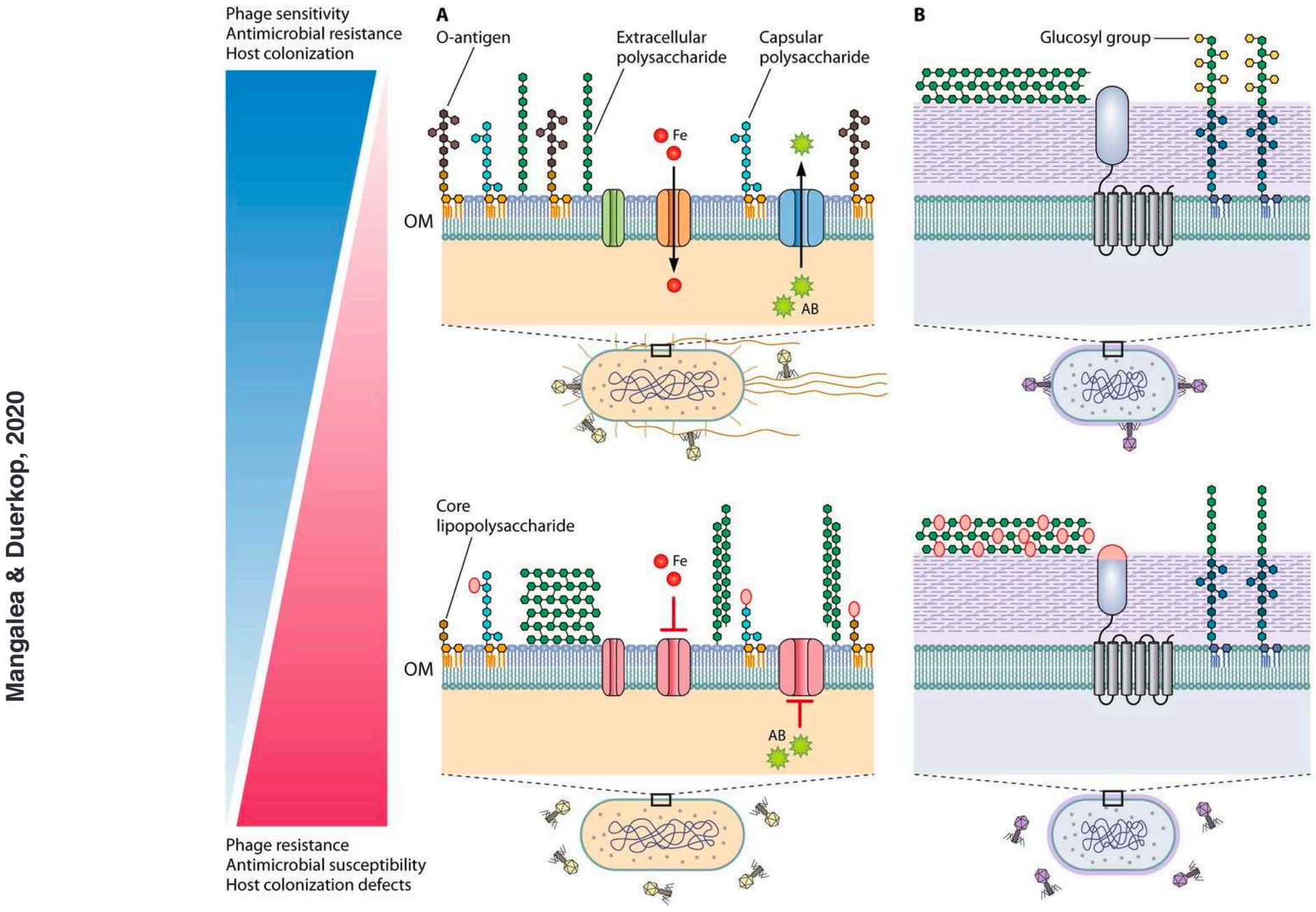
Bacteriophages were discovered independently in 1915 by Frederick Twort, a British pathologist, and in 1917 by Félix d'Hérelle, a French–Canadian microbiologist



a | The specificity of phages can be explored for phage therapy, by which phages target particular bacterial pathogens.
b | Phage products, such as enzymes, can be used to target specific bacteria, including pathogens.
c | Phages can be used to disrupt biofilms, by targeting bacteria embedded in these structures, and can be engineered to release specific enzymes that degrade the biofilm matrix.
d | Phages can be used to sensitize antibiotic-resistant bacteria. For example, phages can introduce antibiotic-sensitive genes into drug-resistant hosts, and this strategy can be combined with antibiotic treatment.

Salmond & Fineran, 2015

Fitness Trade-Offs Resulting from Bacteriophage Resistance Potentiate Synergistic Antibacterial Strategies



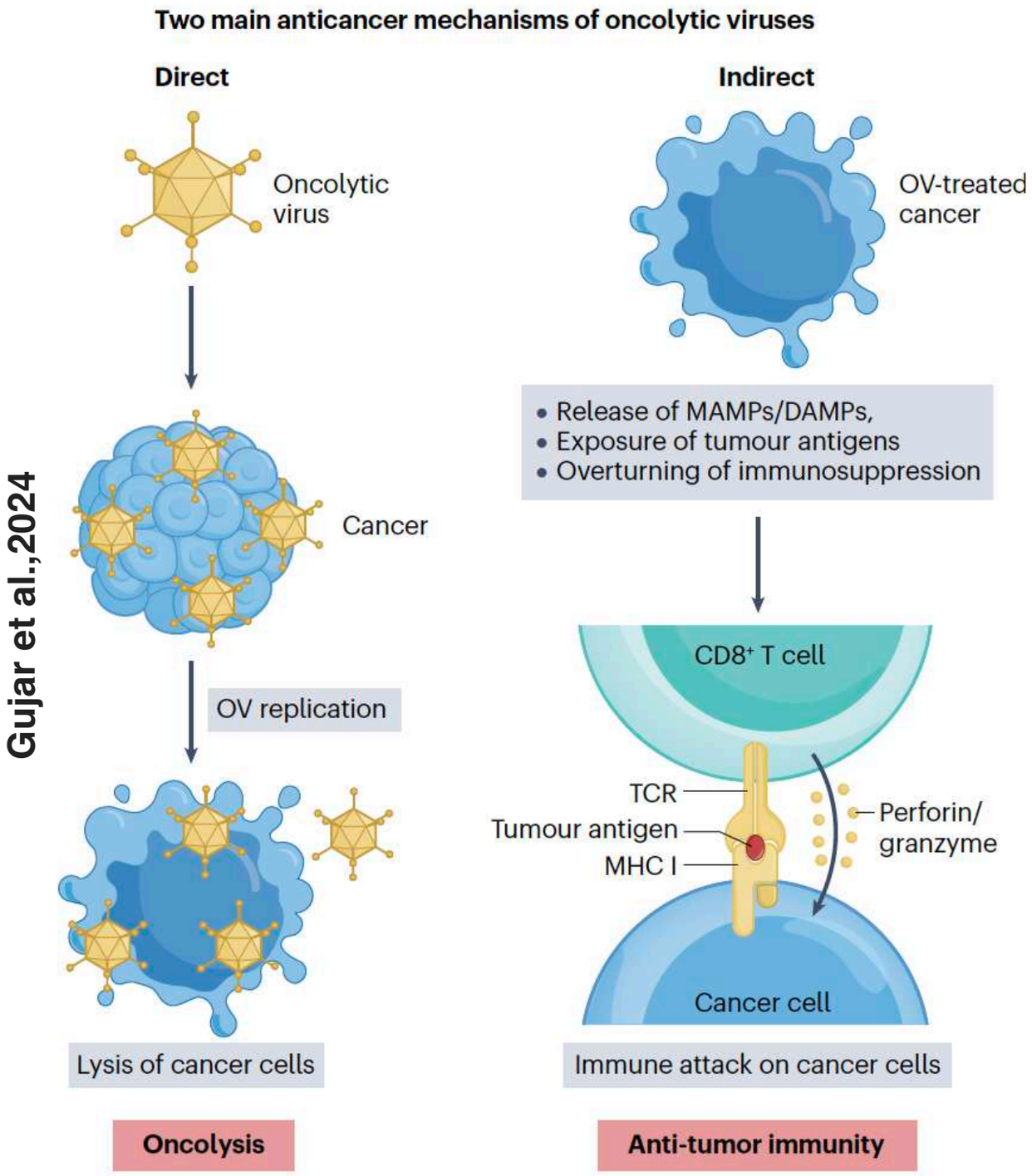
Mangalea & Duerkop, 2020

Bacterial cell surface mutations and modifications produce fitness trade-offs between bacteriophage resistance, antimicrobial susceptibility, and host colonization.

Oncolytic viruses

Oncolytic viruses are naturally occurring or genetically engineered viruses that can **preferentially** infect and kill **transformed or malignant cells** without causing comparable effects in normal, healthy cells

Antitumor mechanisms of oncolytic viruses, I

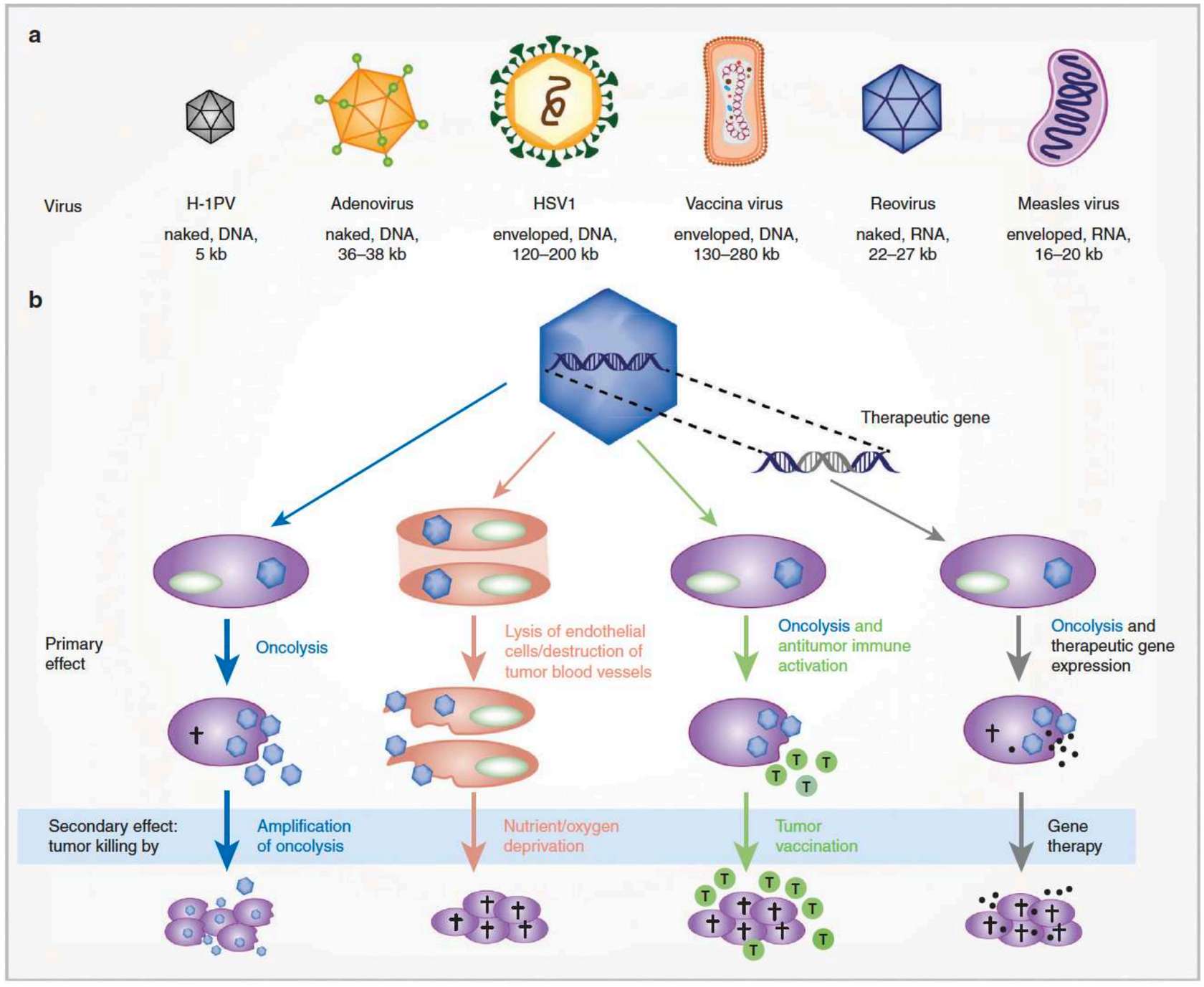


- Two main mechanisms: **direct and indirect**

- In the direct mechanism, oncolytic viruses infect susceptible cancer cells and precipitate their death, a process referred to as '**oncolysis**'

- In the indirect mechanism, oncolytic viral infection triggers a **robust pro-inflammatory response** that releases microorganism-associated molecular patterns (MAMPS) and danger-associated molecular patterns (DAMPs) and overcomes the inherent immunosuppressive mechanisms within the tumor microenvironment

Antitumor mechanisms of oncolytic viruses, II



Ungerechts et al., 2016

Cancer therapy

1842—Long performs surgery under ether anesthesia (111)

1895—Radiotherapy for cancer (6)

1903—1st cured case of cervical cancer by X—rays (6)

1942—Nitrogen mustards introduced as chemotherapeutics (112)

1948—Folic acid antagonists for treatment of leukemia (8)

1958—1st solid tumor cured by chemotherapy (113)

1965—Simultaneous administration of drugs (POMP regimen) induces long term remission in ALL (114)

1968—Stereotactic radio surgery developed (5)

2005—1st approved oncolytic virus (3)

Virology

1798—Jenner develops vaccination for smallpox (115)

1885—Pasteur develops and uses rabies vaccine (116)

1892—Ivanofsky shows TMV is caused by filterable agent (13)

1909—Poliovirus discovered (117)

1915—d'Herelle develops Plaque Assay (17)

1939—1st photographs of viruses with electron microscope (18)

1948—1955—Transition to cell culture for virus propagation and vaccine production (19,20)

1952—Salk develops Polio vaccine (118)

1970—Reverse transcriptase discovered (119)

1981—1st infectious clone of a virus (120)

1985—1st 3D structure of a virus (121)

Kelly & Russel, 2006

Table 1 | Currently approved oncolytic and non-oncolytic viruses worldwide

Name	Virus	Indication	Location	Results from registry studies
H101	Adenovirus	In combination with chemotherapy for patients with nasopharyngeal carcinoma	China (2005)	ORR 72.7% in patients receiving H101 plus chemotherapy versus 40.3% with chemotherapy alone; 28.3% of patients had injection site reactions and 9.8% had influenza-like symptoms[105,106,129,130]
T-VEC	HSV1	Unresectable stage IIIB–IV melanoma	Australia (2016), Europe (2015), Israel (2017), USA (2015)	DRR 16.3% in patients receiving T-VEC versus 2.1% in those receiving GM-CSF, OR 8.9 ($P<0.001$); median OS 23.3 months versus 18.9 months, HR 0.79, 95% CI 0.62–1.00 ($P=0.051$)[4]
ECHO-7[a]	Echovirus	Stage I–II melanoma	Armenia (2016), Georgia (2015), Latvia (2004)	Decreased risk of disease progression with ECHO-7 relative to other experimental immunotherapies, HR 6.67 ($P<0.001$)[131]
Teserpaturev	HSV1	R/R glioblastoma following radiotherapy and temozolomide	Japan (2021)	Median PFS 4.7 months; median OS 20.2 months; grade 3 and 4 adverse events seen in 26.3% and 10.5% of patients, respectively[98,132]
Nadofaragene firadenovec	Adenovirus	BCG-unresponsive non-muscle invasive bladder cancer	USA (2022)	Complete response rate of 51% and median duration of response of 9.7 months when administered by intravesical infusion every 3 months for up to 1 year[113]

BCG, bacillus Calmette–Guerin. DRR, durable response rate; GM-CSF, granulocyte–macrophage colony-stimulating factor; HSV1, herpes simplex virus type 1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R/R residual or recurrent; T-VEC, talimogene laherparepvec. [a]Discontinued owing to manufacturing issues in 2019.

Shalhout et al., 2023

Table 1 | Replication-competent DNA viruses with oncolytic activity

Family	Genome structure, size	Capsid symmetry, naked/ enveloped, virion size	Genus	Species	Natural entry receptors and co-receptors	Cancer[a]	Main strains tested/ approved in the clinic[b]	References
Adenoviridae	dsDNA, 26–45 kb	Icosahedral, naked, Ø 70–100 nm	Mastadenovirus	Human adenovirus B serotype 3	DSG-2, HSPGs, integrin αVβ5 (CD51)	BC, bladder cancer, CRC, lung cancer, neuroblastoma, ovarian cancer, pancreatic cancer, prostate cancer, sarcoma, thyroid cancer	Ad3-hTERT-E1A	231–238
				Human adenovirus B serotype 7	DSG-2, HSPGs, integrin αVβ5 (CD51)	HCC, lung cancer, melanoma, myeloma		233,238, 239
				Human adenovirus B serotype 11	CD46, DSG-2, HSPGs, integrin αVβ5 (CD51)	CRC, HCC, lung cancer, melanoma, ovarian cancer	Colo-Ad1 (enadenotucirev, EnAd), NG-350, NG-641	233, 238–242
				Human adenovirus B serotype 35	CD46, HSPGs, integrin αVβ5 (CD51)	Bladder cancer, HCC, lung cancer, melanoma	–	233,238, 239,243
				Human adenovirus C serotype 1	CAR, HSPGs, integrin α3β1 (CD49c/CD29), integrin αVβ1, integrin αVβ5 (CD51)	CRC, HCC, Lung cancer, osteosarcoma, pancreatic cancer	–	238,244
				Human adenovirus C serotype 2	CAR, HSPGs, integrin α3β1 (CD49c/CD29), integrin αMβ2 (CD11b/CD18), integrin αVβ1, integrin αVβ5 (CD51)	CRC, HCC, lung cancer, osteosarcoma, pancreatic cancer	–	238,244

	(CD51)			
Human adenovirus C serotype 5	CAR, HSPGs, integrin α3β1 (CD49c/CD29), integrin αVβ1, integrin αVβ5 (CD51)	BC, bladder cancer, iCCA, cervical cancer, CRC, gastric cancer, glioma, HER2⁺ tumors, HCC, HNC, lung cancer, melanoma, myeloma, neuroectodermal tumors, osteosarcoma, ovarian cancer, osteosarcoma, pancreatic cancer, prostate cancer	Ad5-yCD/mutTK(SR39) rep-ADP, Ad5-yCD/ mutTKSR39rep-hIL12, AdAPT-001, Ad-TD-nsIL12, AdVince (ELC-100), cretostimogene grenadenorepvec (CG0070), CG7870 (CV787), CGTG-602, CV706, DNX-2401 (Delta-24-RGD; tasadenoturev), DNX-2440 (delta-24-RGDOX), ICOVIR-5, ICOVIR-7, LOAd703, L-IFN (YSCH-01) c, MEM-288c, OBP-301 (telomelysin), Onc.Ad5 (in CAdVEC combination regimen), **Oncorine (H101)**, ONCOS-102 (CGTG-102),ONYX-015 (dl1520), ORCA-010, PeptiCRAd-1, Surv.m-CRA, TILT-123 (Ad5/3-E2F-D24-hTNFa-IRES-hIL2), VALO-D102 (Ad5/3-D24-OX40L-CD40L), VCN-01	223,238, 239,245–263
Human adenovirus C serotype 6	CAR, HSPGs, integrin α3β1 (CD49c/CD29), integrin αVβ1, integrin αVβ5 (CD51)	CRC, HCC, lung cancer, myeloma, osteosarcoma, pancreatic cancer	–	264–267
Human adenovirus D serotype 10	CAR, sialic acids	BC, CRC	–	264,268
Human adenovirus D serotype 17	CAR, CD46, sialic acids	HCC, lymphoma, myeloma	–	264, 265,269

Family	Genome structure, size	Capsid symmetry, naked/ enveloped, virion size	Genus	Species	Natural entry receptors and co-receptors	Cancer[a]	Main strains tested/ approved in the clinic[b]	References
				Human adenovirus D serotype 24	CAR, CD46, sialic acids	HCC, lymphoma, myeloma		264, 265,269
				Human adenovirus D serotype 26	CAR, CD46, integrin αVβ3 (CD61), sialic acids	BC, cervical cancer, HCC, leukemia, lung cancer, lymphoma, myeloma, ovarian cancer	–	264,265, 269,270
				Human adenovirus D serotype 28	CAR, CD46, sialic acids	BC, cervical cancer, HCC, lung cancer, lymphoma, myeloma, ovarian cancer	–	264,265, 269,270
				Human adenovirus D serotype 30	CAR, sialic acids	HCC, lymphoma, myeloma	–	264,265
				Human adenovirus D serotype 45	CAR, CD46, sialic acids	BC, cervical cancer, HCC, lung cancer, lymphoma, myeloma, ovarian cancer	–	264,265, 269,270
				Human adenovirus D serotype 48	CAR, CD46, sialic acids	BC, cervical cancer, HCC, leukemia, lung cancer, lymphoma, myeloma, ovarian cancer	–	264,265, 269,270
				Human adenovirus E serotype 4	CAR	HCC, myeloma	–	264,265

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				serotype 4				
Herpesviridae	dsDNA, 135–155 kb	Icosahedral, enveloped, Ø155–240 nm	Simplexvirus	Herpes simplex virus 1	HSPGs, HVEM, MAG, nectin-1, NMHC-IIA, PILRα	BC, bladder cancer, CRC, embryonal tumor, glioma, HCC, HNC, lung cancer, lymphoma, melanoma, mesothelioma, neuroblastoma, non-melanoma skin cancers, ovarian cancer, pancreatic cancer, neuroectodermal tumor, prostate cancer, sarcoma	C134 (MB-108), **G47Δ (teserpaturev, Delytact)**, G207, TBI-1401 (HF10, canerpaturev, C-REV), HSV1716 (Seprehvir), M032, MVR-C5252, MVR-T3011, NV1020, ONCR-177, ONCR-GBM, OrienX010, RP1 (vusolimogene oderparepvec), RP2, RP3, rQNestin34.5v.2 (CAN-3110), rRp450, STI-1386 (Seprehvec), **T-VEC (talimogene laherparepvec, IMLYGIC, OncoVEXGM-CSF)**, VG161	47,246, 247,252, 255,260, 264,271–277
				Herpes simplex virus 2	HVEM, nectin-1, nectin-2	Cervical cancer, CRC, GI cancers, glioma, HCC, HNC, mammary cancer, melanoma, ovarian cancer, pancreatic cancer, soft tissue sarcomas	OH2 (BS-001, rHSV2hGM-CSF)	276–281
			Varicellovirus	Bovine herpesvirus 1	HSPGs, nectin-1, PILRα, PVR (CD155)	CNS cancer, CRC, HCC, leukemia, lung cancer, mammary cancer, melanoma, ovarian cancer, prostate cancer, RCC	–	282–284
				Suid herpesvirus 1 (pseudorabies virus)	Nectin-1	Bladder cancer, intestinal cancer	–	285–287
			Rhadinovirus	Bovine herpesvirus 4	ND	BC, glioma, lung cancer, ovarian cancer	–	210, 288,289
				Herpesvirus saimiri	ND	CRC, pancreatic cancer	–	290,291

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Table 1 (continued) | Replication-competent DNA viruses with oncolytic activity

Family	Genome structure, size	Capsid symmetry, naked/ enveloped, virion size	Genus	Species	Natural entry receptors and co-receptors	Cancer[a]	Main strains tested/ approved in the clinic[b]	References
Parvoviridae	ssDNA, 4–6 kb	Icosahedral, naked, Ø 25–30 nm	Parvovirus	H-1	Sialic acids (e.g., on laminin)	BC, blastoma, cervical cancer, CRC, gastric cancer, glioma, HCC, leukemia, lymphoma, melanoma, pancreatic cancer, sarcoma	ParvOryx (H-1PV)	23,271, 292–302
				LuIII	ND	Glioma	–	301
				Minute virus of mice	Sialic acids	Glioma	–	303,304

Poxviridae	dsDNA, 135–230 kb	Complex, enveloped, 160–340 × 260–380 nm	Orthopoxvirus	Cowpox virus	HSPGs, laminin	Cervical cancer, CRC, glioma, HCC, lung cancer	–	305–307
				Vaccinia virus	HSPGs, laminin, MARCO, TAM receptors	BC, bladder cancer, cervical cancer, CRC, fallopian tube cancer, glioma, HCC, HNC, leukemia, lung cancer, lymphoma, melanoma, mesothelioma, myeloma, neuroendocrine cancer, non-melanoma skin cancer, ovarian cancer, pancreatic cancer, peritoneal cancer, prostate cancer, RCC, sarcoma	ASP9801, BT-001 (TG6030, VVcopTK-RR-), CF33-hNIS (VAXINIA), CF33-hNIS-anti-PD-L1 (CHECKvacc), Olvi-Vec (olvimulogene nanivacirepvec, GL-ONC1, GLV-1h68), Pexa-Vec (pexastimogene devacirepvec, JX-594), RGV004, Tbio-6517 (TAK-605, RIVAL-01), TG6002 (T601), vvDD	76,246, 247,271, 306–322
				Raccoonpox virus	ND	Cervical cancer, CRC, glioma, HCC, lung cancer, pancreatic cancer	–	323,324
			Oryzopoxvirus	Cotia virus	ND	Cervical cancer, glioma	–	323
			Parapoxvirus	ORF virus (parapoxvirus ovis)	ND	Cervical cancer, CRC, glioma, lung cancer, melanoma, pancreatic cancer	–	323, 325,326
			Leporipoxvirus	Myxomavirus	ND	Cervical cancer, CRC, glioma, leukemia	–	317,323, 327–329
				Squirrel fibroma virus	ND	HCC, gastric cancer, glioma, lung cancer	–	317,323
			Suipoxvirus	Swinepox virus	ND	Cervical cancer, glioma	–	323
			Yatapoxvirus	Yaba-like disease virus	ND	Cervical cancer, glioma, ovarian cancer	–	317, 323,330

BC, breast (or mammary) cancer; CNS, central nervous system; CRC, colorectal cancer; ds, double-stranded; GI, gastrointestinal; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HSPGs, heparan sulfate proteoglycans; HVEM, herpesvirus entry mediator; iCCA, intrahepatic cholangiocarcinoma; ND, not determined; RCC, renal cell carcinoma; ss, single-stranded; TAM receptors, Tyro3/Axl/Mer receptors; Ø, diameter. [a]Examples of application reported in vitro and/or in vivo in preclinical models and clinical trials. [b]Strains shown in bold have been approved. [c]Presumed to be of serotype 5 backbone, but information not communicated.

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Table 2 | Replication-competent RNA viruses with oncolytic activity

Family	Genome structure, size	Capsid symmetry, naked/ enveloped, virion size	Genus	Species	Natural entry receptors and co-receptors	Cancer[a]	Main strains tested in the clinic	References
Coronaviridae	(+) ssRNA, 26–32 kb	Helical, enveloped, Ø 80–220 nm	Coronavirus	Feline infectious peritonitis virus	APN, DC-SIGN	$EGFR^+$ tumors, cervical cancer, CRC, epidermoid cancer, HCC, intestinal cancer, ovarian cancer	–	331–333
				Mouse hepatitis virus	CEACAM1	$EGFR^+$ tumors, cervical cancer, CRC, epidermoid cancer, glioma, HCC, intestinal cancer, ovarian cancer	–	331, 334–336
Flaviviridae	(+) ssRNA, 11 kb	Icosahedral, enveloped, Ø 40–65 nm	Flavivirus	Zika virus	DC-SIGN, HSPGs, TIM-1	Glioma	–	252, 337–339
Orthomyxoviridae	(–) ssRNA, segmented, 13–19 kb	Helical, enveloped, Ø 80–120 nm	Influenzavirus	Influenza A virus	DC-SIGN, FFR2, MHC-II, sialic acids (e.g., on proteins Cav1.2, EGFR or nucleolin)	CRC, HCC, lung cancer, melanoma, pancreatic cancer	–	243, 340–347
Paramyxoviridae	(–) ssRNA, 15–20 kb	Helical, enveloped, Ø 120–350 nm	Avulavirus	Newcastle disease virus	Sialic acids	BC, bladder carcinoma, cervical carcinoma, CRC, epidermoid cancer, fibrosarcoma, glioma, HCC, HNC, lung cancer, melanoma, neuroblastoma, Osteosarcoma, prostate cancer, RCC, Wilm's tumor	MEDI5395, MTH-68/H, PV701	247, 348–358
			Morbillivirus	Canine distemper virus	Nectin-4, SLAM (CD150)	Cervical cancer, leukemia, lymphoma, mammary cancer, sarcoma	–	359–362
				Measles virus	CD46, SLAM (CD150)	BC, CRC, glioma, leukemia, lung cancer, lymphoma, melanoma, mesothelioma, myeloma, ovarian cancer, pancreatic cancer, prostate cancer	MV-CEA, MV-NIS	246,247, 271,354, 363–372
			Respirovirus	Murine respirovirus (Sendai virus)	Sialic acids (e.g., on proteins ASGR1, CD235a or GP2 or gangliosides)	Fibrosarcoma, HNC, lung cancer, mastocytoma, pancreatic cancer, prostate cancer, RCC	–	354,373–384
			Rubulavirus	Mumps virus	Sialic acids	BC, CRC, HNC, lung cancer, myeloma, neuroblastoma, prostate cancer	–	354, 385–387
				Simian virus 5	Sialic acids	Lung cancer, prostate cancer	–	388–390

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Picornaviridae	(+) ssRNA, 7–8 kb	Icosahedral, naked, Ø 30 nm	Cardiovirus	Encephalomyocarditis virus (mengovirus)	HSPGs, sialic acids	BC, cervical cancer, CRC, glioma, HCC, lung cancer, leukemia, lymphoma, melanoma, myeloma, ovarian cancer, pancreatic cancer, plasmacytoma, prostate cancer, RCC	–	391–396
			Enterovirus	Bovine enterovirus 1	ND	BC, leukemia, sarcoma	–	397–399
				Coxsackievirus A13	ICAM-1	Melanoma	–	400,401
				Coxsackievirus A15	ND	Melanoma	–	400
				Coxsackievirus A18	ICAM-1	Melanoma	–	400,401
				Coxsackievirus A21	DAF (CD55), ICAM-1	BC, bladder cancer, HNC, lung cancer, melanoma, prostate cancer, RCC	Gebasaxturev (CAVATAK, V937, CVA21)	247, 401–405
				Coxsackievirus B3	CAR, DAF	BC, CRC, endometrial cancer, lung cancer	–	406–408

Table 2 (continued) | Replication-competent RNA viruses with oncolytic activity

Family	Genome structure, size	Capsid symmetry, naked/ enveloped, virion size	Genus	Species	Natural entry receptors and co-receptors	Cancer[a]	Main strains tested in the clinic	References
				Poliovirus	PVR (CD155)	BC, glioma, prostate cancer, sarcoma	Lerapolturev (PVSRIPO)	247,271, 401, 409–413
				Echovirus 1	Integrin α2β1	Gastric cancer, ovarian cancer, prostate cancer	–	401, 414–416
				Echovirus 7	DAF (CD55)	Cervical cancer, CRC, glioma, HCC, lung cancer, melanoma, RCC, sarcoma	RIGVIR (ECHO-7)	416–420
				Echovirus 12	DAF (CD55)	CRC	–	416,421
				Echovirus 17	ND	CRC	–	421
				Echovirus 26	*ND*	CRC	–	421
				Echovirus 30	DAF (CD55)	Glioma, neuroblastoma	–	416,422
				Enterovirus A71	Annexin II, fibronectin, HSPGs, nucleolin, PSGL1 (CD162), SCARB2, sialic acid, vimentin	Glioma	–	423–426
			Senecavirus	Seneca Valley virus	ANTXR1	Glioma, lung cancer, NETs, neuroblastoma, medulloblastoma, retinoblastoma, rhabdomyosarcoma	NTX-010 (SVV-001)	247, 427–432
Reoviridae	dsRNA, segmented, 18–30 kb	Icosahedral, naked, Ø 60–80 nm	Orbivirus	Bluetongue virus-10	Sialic acids (e.g., on glycophorin A)	HCC, lung cancer	–	433–437
			Orthoreovirus	Reovirus serotype 3	β1 integrins, JAM-A, sialic acids (e.g., on glycophorin A)	BC, CRC, gastric cancer, glioma, HNC, leukemia, lung cancer, melanoma, myeloma, ovarian cancer, pancreatic cancer, peritoneal cancer, prostate cancer, sarcoma	Pelareorep (REOLYSIN)	247,271, 438–441
Retroviridae	(+) ssRNA, 1–2 copies, 7–12 kb	Helical, enveloped, Ø 80–100 nm	Gammaretrovirus	Moloney (ecotropic) murine leukemia virus	Slc7a1 (mCAT1) on rodent cells	BC, CRC, glioma, lung cancer, meduloblastoma, pancreatic cancer	Vocimagene amiretrorepvec (Toca 511, DB107)	271, 442–447
			Spumavirus	Foamy virus	HSPGs	Glioma, lung cancer, ovarian cancer, pancreatic cancer	–	448–450

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						cancer		
Rhabdoviridae	(–) ssRNA, 11–15 kb	Helical, enveloped, 70–75 × 170–200 nm	Vesiculovirus	Bahia Grande virus	ND	CNS, CRC, ovarian cancer	–	320
				Carajas virus	ND	BC, CNS, CRC, lung cancer, melanoma, ovarian cancer, prostate cancer, RCC	–	320
				Farmington virus	ND	BC, CNS cancer, CRC, lung cancer, melanoma, ovarian cancer, prostate cancer, RCC	–	320
				Maraba virus	LDLR	BC, CNS, CRC, HPV$^+$ tumors, lung cancer, melanoma, ovarian cancer, prostate cancer, RCC	MG1E6E7, MG1MA3	34,75, 85,320, 451–453
				Muir Springs virus	ND	CNS cancer	–	320
				Tibrogargan virus	ND	CNS cancer, ovarian cancer	–	320
				Vesicular stomatitis virus	LDLR	BC, CNS cancer, CRC, endometrial cancer, HCC, leukemia, lung cancer, melanoma, myeloma, ovarian cancer, prostate cancer, RCC	VSV-GP (BI 1831169), VSV-GP128, VSV-IFNβ-NIS (Voyager V1, VV1), VSV-hIFNβTYRP1	80–82, 86, 454–463

Table 2 (continued) | Replication-competent RNA viruses with oncolytic activity

Family	Genome structure, size	Capsid symmetry, naked/ enveloped, virion size	Genus	Species	Natural entry receptors and co-receptors	Cancer[a]	Main strains tested in the clinic	References
Togaviridae	(+) ssRNA, 11–12 kb	Icosahedral, enveloped, Ø 50–70 nm	Alphavirus	Getah virus-like M1	HSPGs	BC, bladder cancer, cervical cancer, CRC, glioma, HCC, pancreatic cancer	–	464–468
				Semliki Forest virus	ApoER2, DC-SIGN, HSPGs, L-SIGN, MXRA8, VLDLR	Cervical cancer, CRC, glioma, HCC, lung cancer, melanoma, neuroblastoma, osteosarcoma, prostate cancer, teratocarcinoma	–	53,464, 469–481
				Sindbis virus	ApoER2, CD147, DC-SIGN, HSPGs, LAMR, L-SIGN, NRAMP1/ NRAMP2, PSR, VLDLR	Cervical cancer, CRC, HNC, neuroblastoma, ovarian cancer, prostate cancer, RCC	–	32,464, 478–493

BC, breast (or mammary) cancer; CNS, central nervous system; CRC, colorectal cancer; DAF, decay acceleration factor; DC-SIGN, dendritic cell-specific intracellular adhesion molecule 3-grabbing nonintegrin; ds, double-stranded; GI, gastrointestinal; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HPV, human papilloma virus; HSPGs, heparan sulfate proteoglycans; MV-CEA, carcinoembryonic antigen-expressing oncolytic measles virus derivative; MV-NIS, sodium iodide symporter-expressing oncolytic measles virus; ND, not determined; NETs, neuroendocrine tumours; RCC, renal cell carcinoma; ss, single-stranded. [a]Examples of application reported in vitro and/or in vivo in preclinical models and clinical trials.