ANTIVIRAL

infectious agents

bacteria

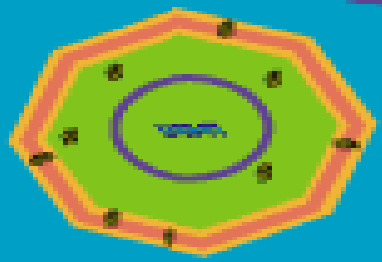
viruses

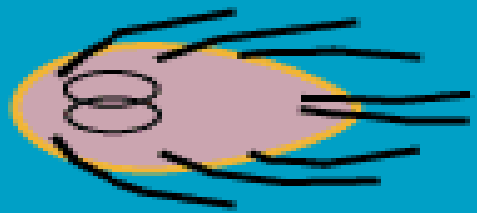
fungi

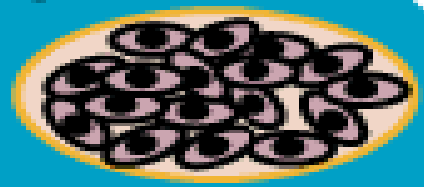
parasites

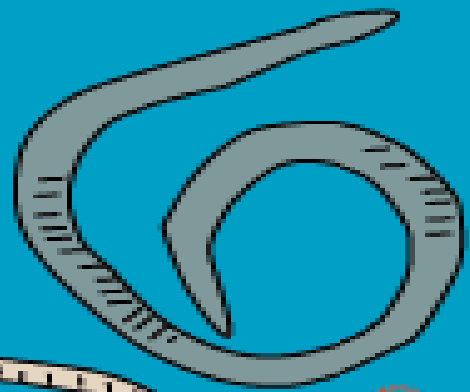
protozoa

helminths
(worms)

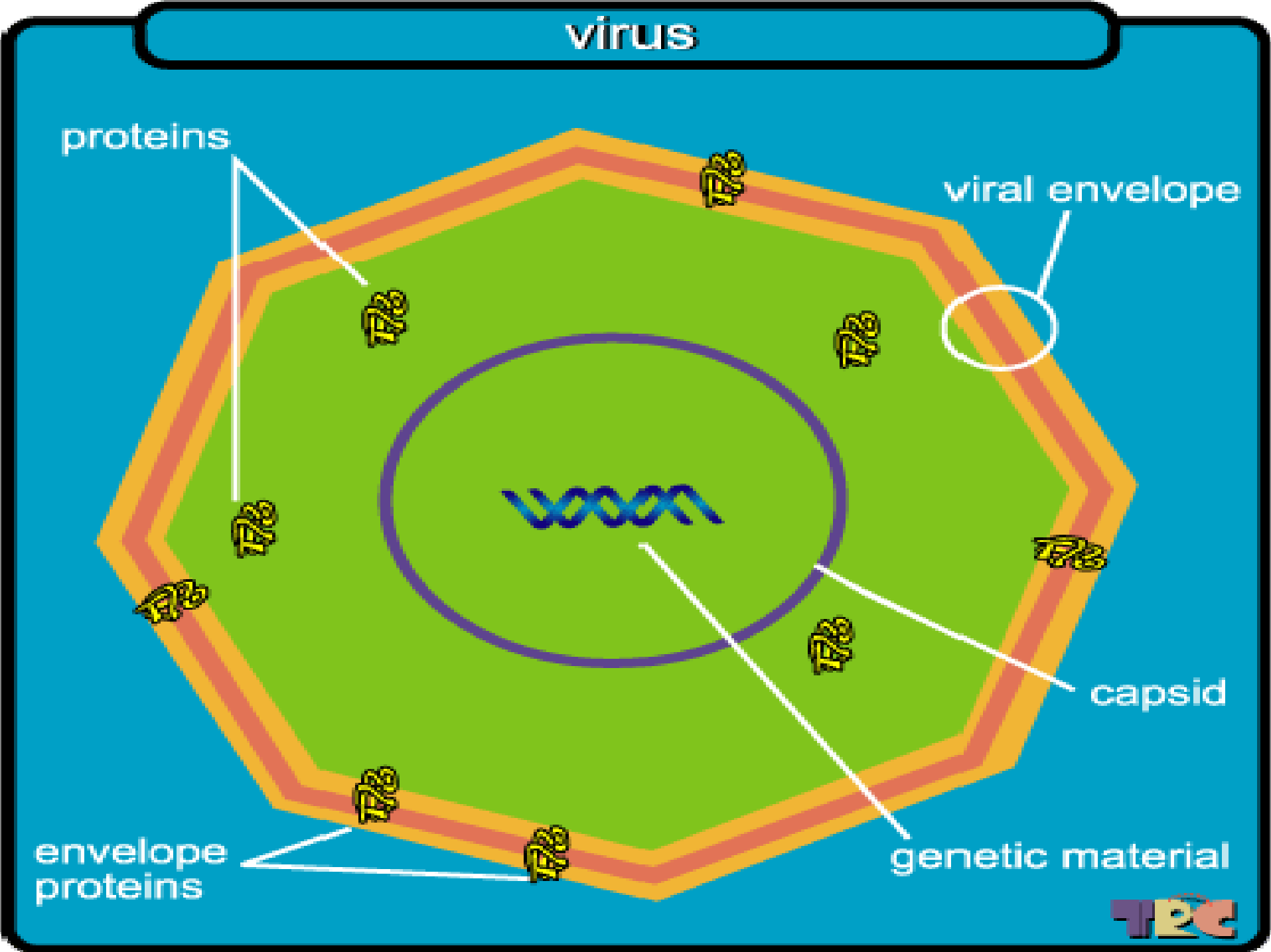


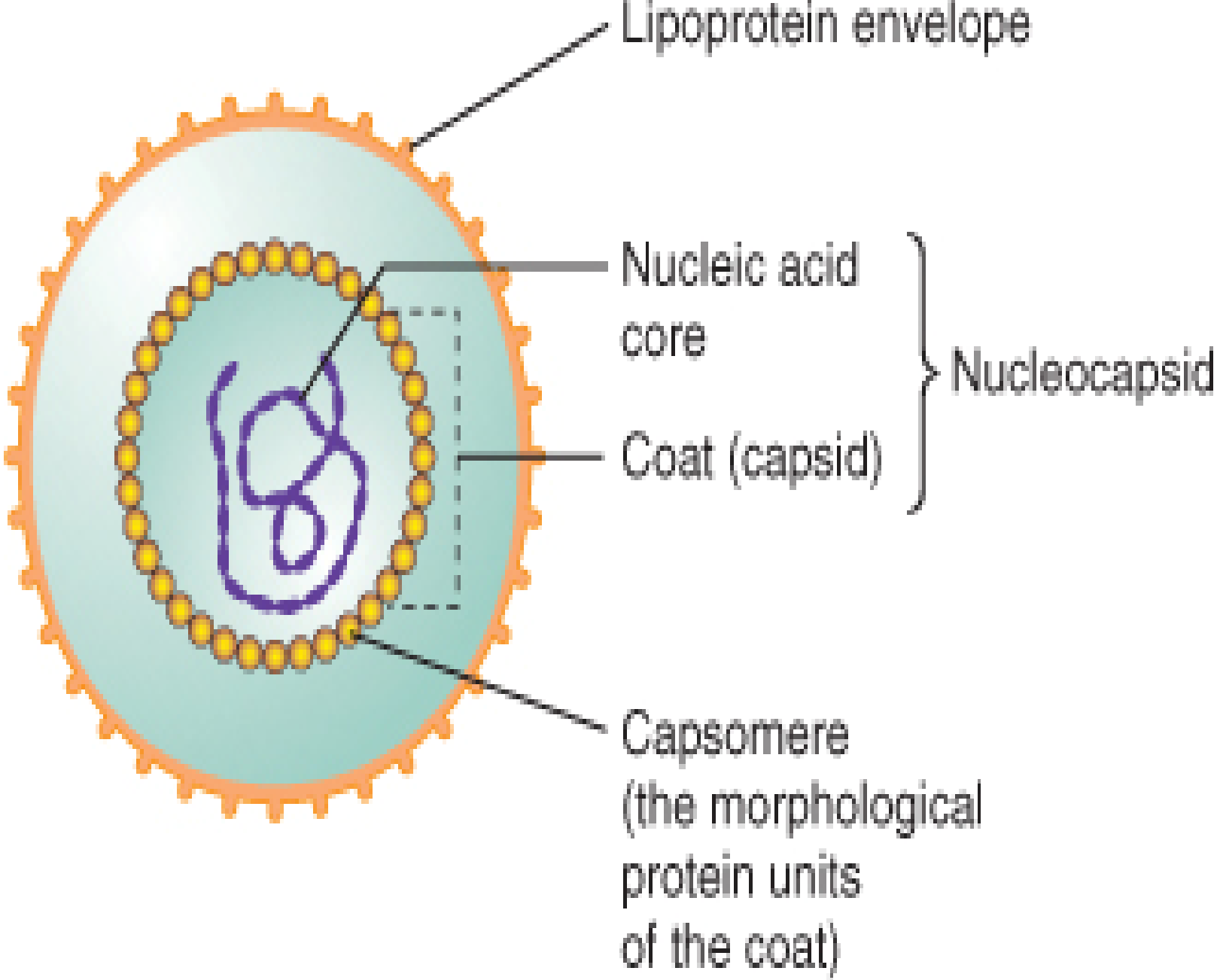






virus


proteins
viral envelope
capsid
genetic material
envelope proteins

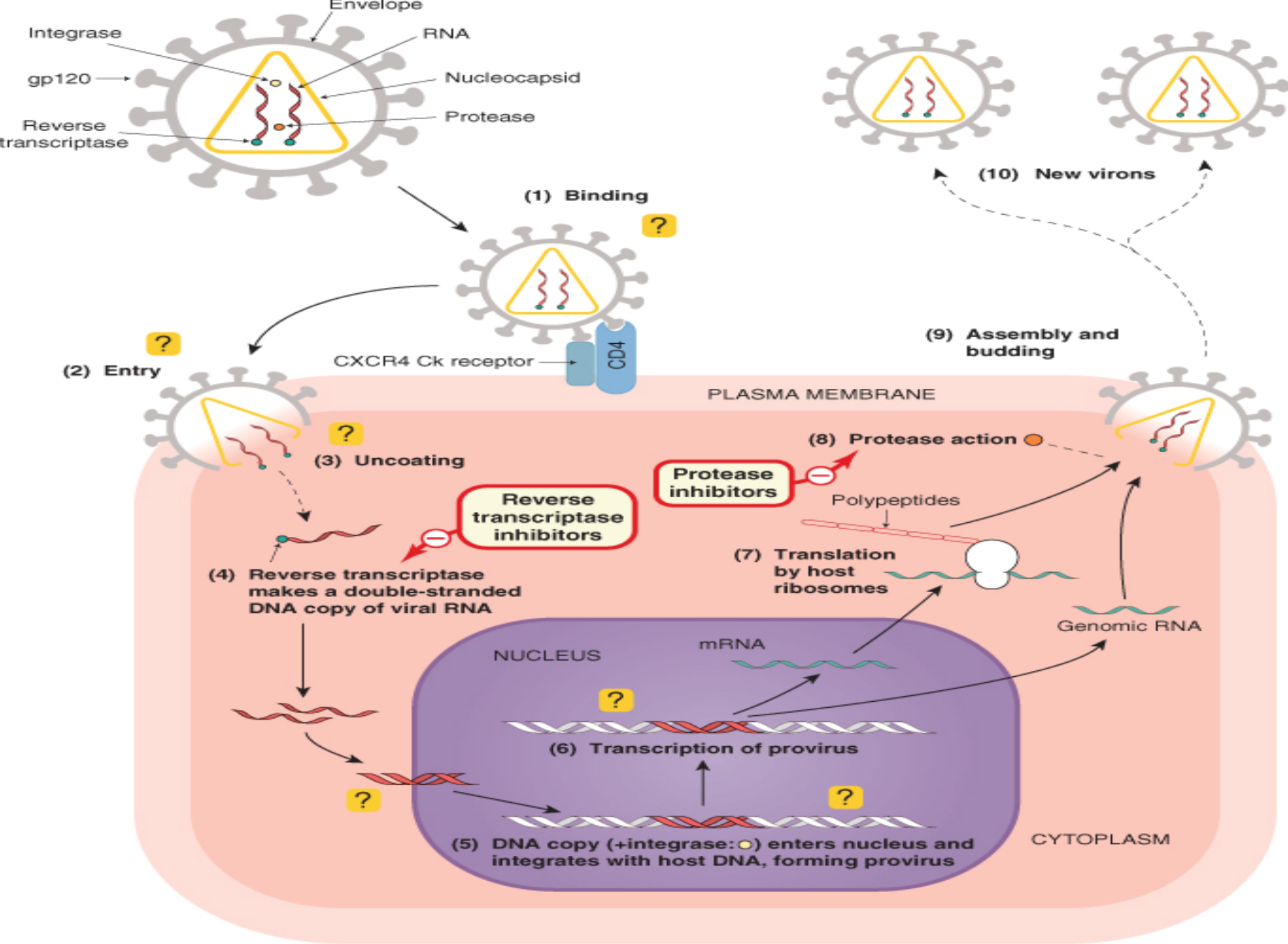


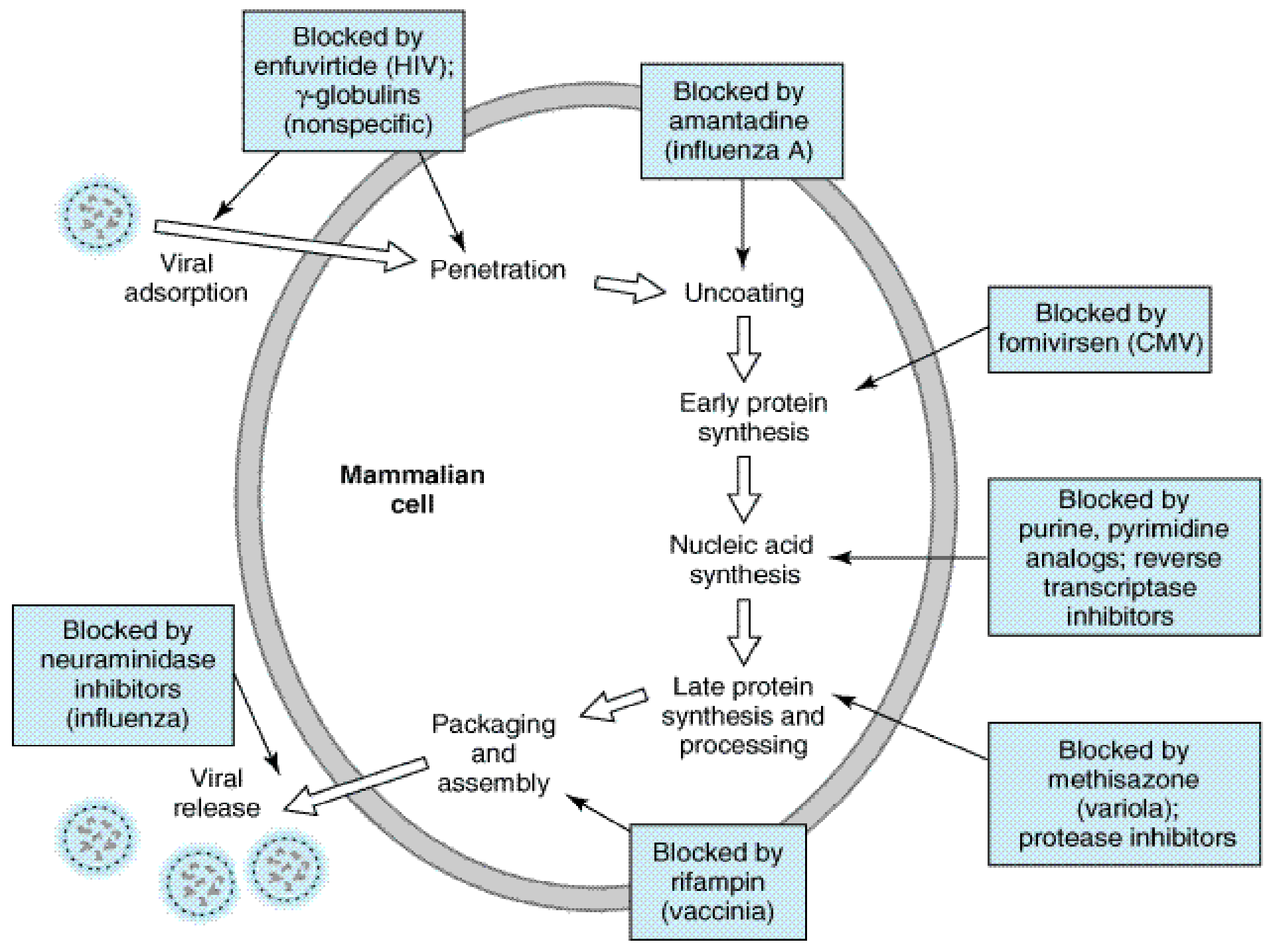
Viruses

- **Viruses consist of genetic material (DNA, positive RNA or negative RNA) packaged into a nucleocapsid and/or membrane.**
- **Unlike other infectious agents, viruses are so small that they depend on the host cell machinery for protein synthesis, energy and replication.**
- **Classification of viruses is based on their genetic material, envelope and/or nucleocapsid, size and morphology.**

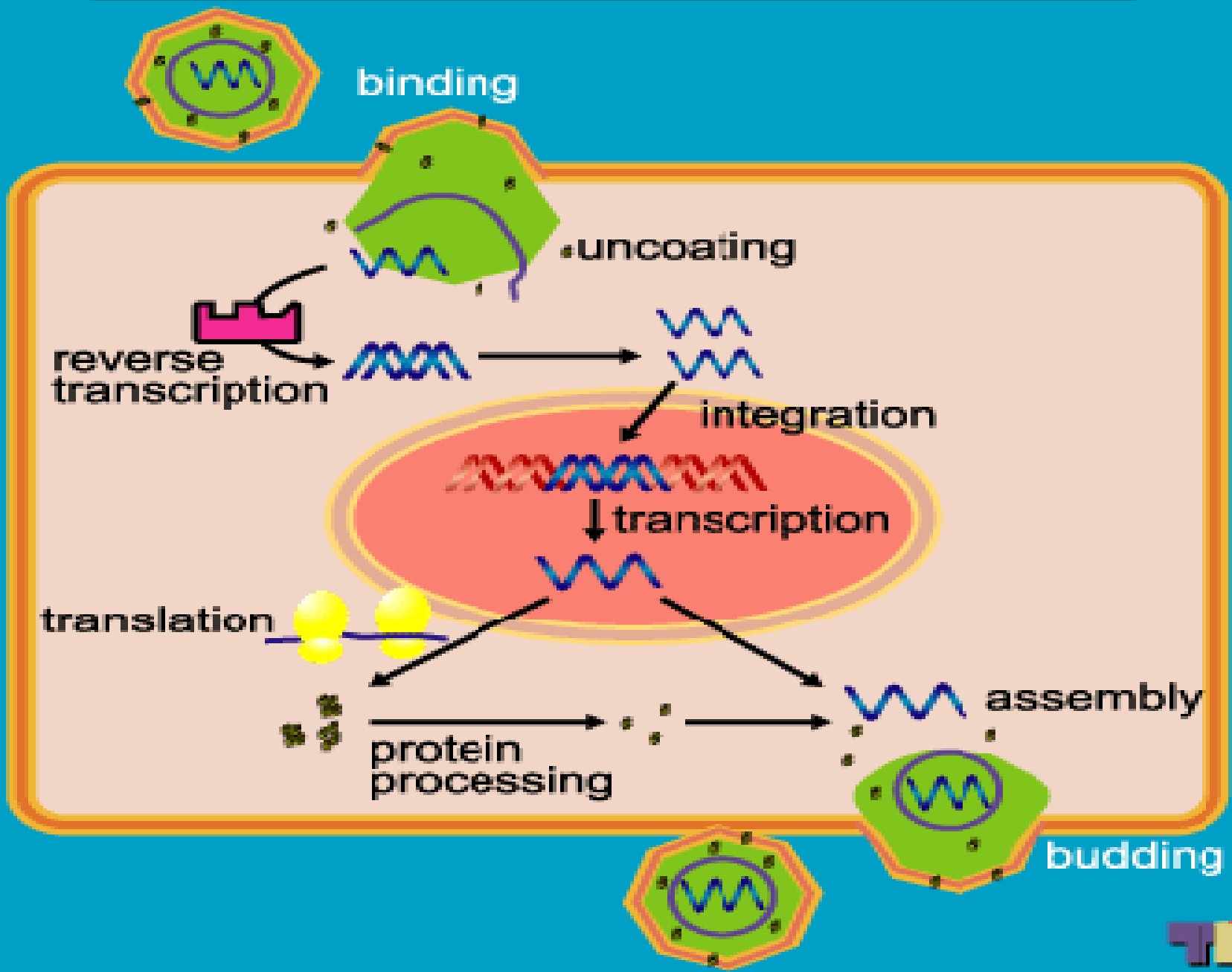
Viral replication consists of several steps:

- **(1) adsorption to and penetration into susceptible host cells;**
- **(2) uncoating of viral nucleic acid;**
- **(3) synthesis of early regulatory proteins, eg, nucleic acid polymerases;**
- **(4) synthesis of RNA or DNA;**
- **(5) synthesis of late, structural proteins;**
- **(6) assembly (maturation) of viral particles;**
- **(7) release from the cell. Antiviral agents can potentially target any of these steps**




Blocked by enfuvirtide (HIV); γ-globulins (nonspecific)
Blocked by amantadine (influenza A)
Viral adsorption
Penetration
Uncoating
Blocked by fomivirsen (CMV)
Early protein synthesis
Mammalian cell
Nucleic acid synthesis
Blocked by purine, pyrimidine analogs; reverse transcriptase inhibitors
Blocked by neuraminidase inhibitors (influenza)
Late protein synthesis and processing
Packaging and assembly
Viral release
Blocked by methisazone (variola); protease inhibitors
Blocked by rifampin (vaccinia)

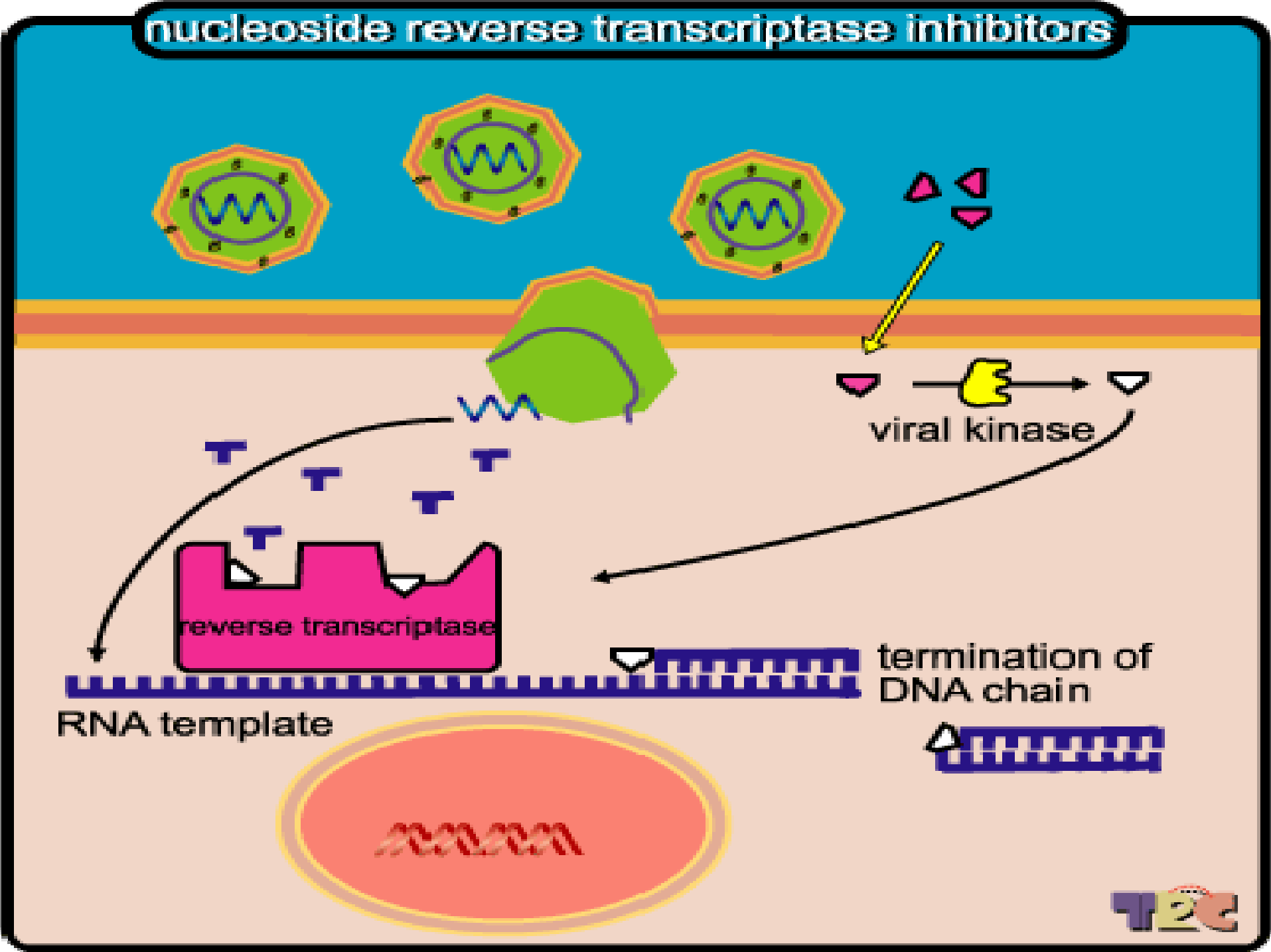
retrovirus replicative cycle



Retrovirus replicative cycle

- **The retroviruses, like HIV, bind to the host cell membrane and enter the cell by endocytosis.**
- **Their RNA is reverse transcribed into DNA, which is integrated in the host cell genome.**
- **The integrated viral DNA is transcribed into new viral RNA and mRNA for viral protein synthesis.**
- **The assembly of viral components occurs in the cytoplasm and the new viruses are released from the host cell by budding.**

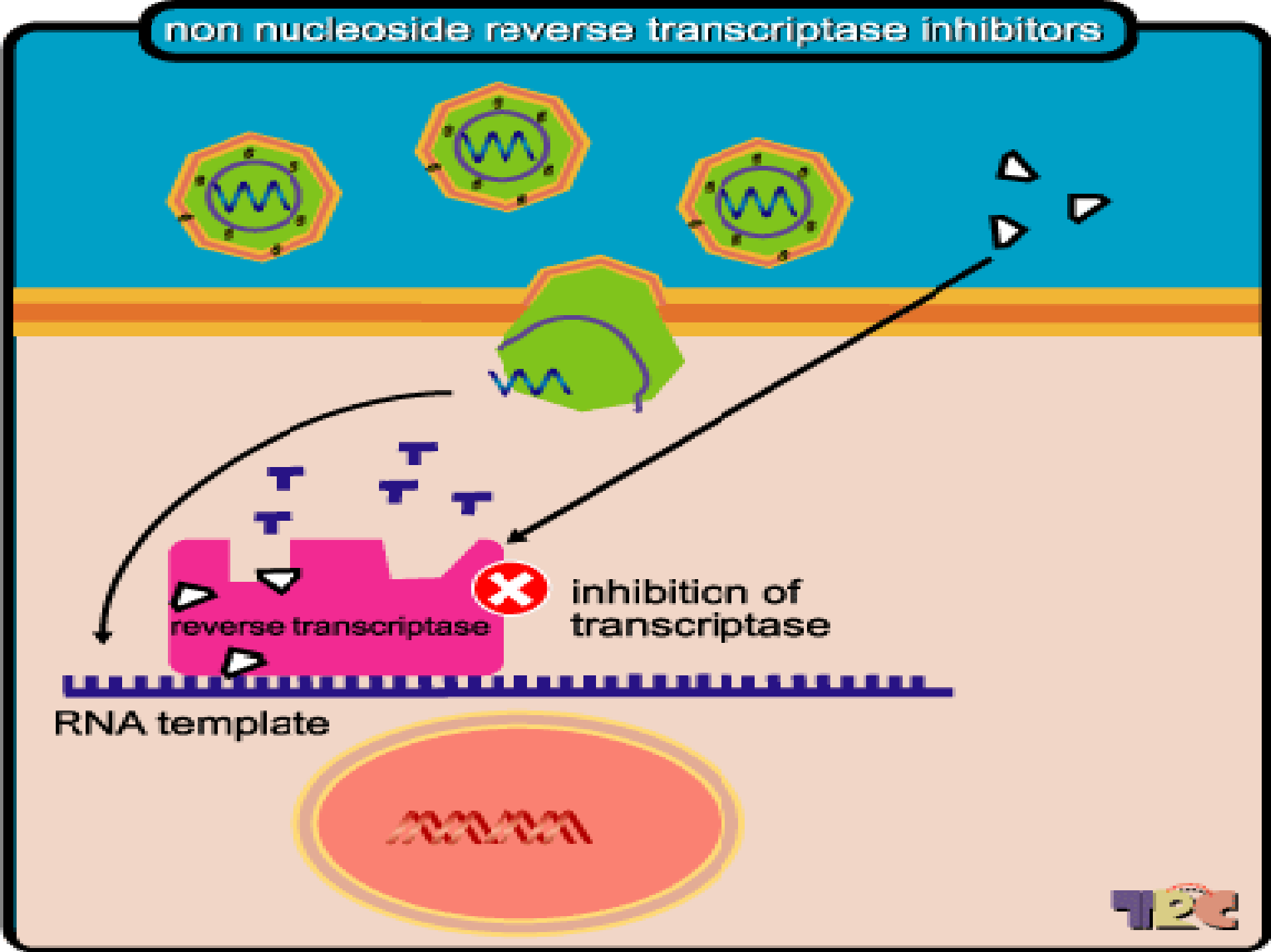
- **HIV therapy involves a combination of *antiretroviral drugs* (HAART therapy):**
  - **2 NRTIs**
  - **or a NRTI + a NNRTI**
  - **or a NRTI + a protease inhibitor.**
- **Recently, immunotherapy (IL-2, interferon) for HIV has gained interest. However, there is still no proof of clinical benefit.**


nucleoside reverse transcriptase inhibitors
viral kinase
reverse transcriptase
termination of DNA chain
RNA template

NRTI

- Nucleoside reverse transcriptase inhibitors (NRTIs) are analogues of the natural RNA and DNA nucleotides.
- *Zidovudine* (AZT) e.g. is a thymidine analogue. This drug is phosphorylated three times, like its natural analogue and together they compete for the reverse transcriptase.
- The triphosphate drug inhibits the reverse transcriptase. However when transcription still occurs, the triphosphate drug is built in the DNA. The incorporation of nucleoside analogues aborts DNA synthesis and destabilizes the viral double DNA strand.
- Zidovudine was the first antiretroviral agent.
- In high doses it can lead to severe myelotoxicity, but in normal doses it causes only some initial gastrointestinal complaints.
- Zidovudine is a favorable NRTI because it lacks neurotoxicity and good CNS penetration.
  Lamivudine (3TC) is another well-tolerated nucleoside analogue. Its disadvantage is a rapid development of resistance. **Lamivudine** is also effective against **Hepatitis B viruses**.

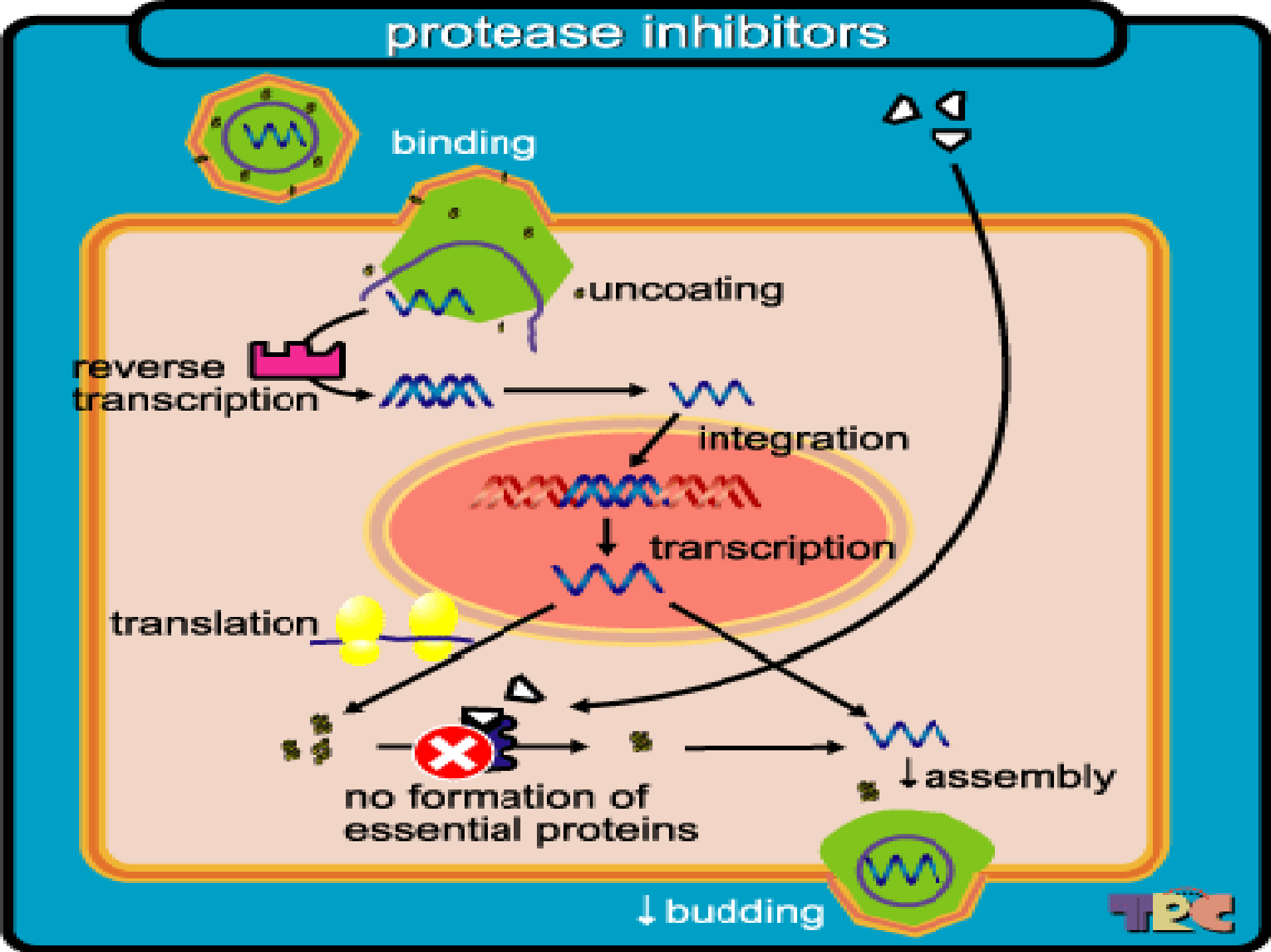
non nucleoside reverse transcriptase inhibitors



NNRTI

- ***Nevirapine***, ***delavirdine*** **and** ***efavirenz*** **➔ Non-nucleoside reverse transcriptase inhibitors (NNRTIs).**
- **They bind directly and non-competitively to the reverse transcriptase of HIV and block the polymerase activity by deregulating the catalytic part of the enzyme.**
- **In contrast to NRTIs, NNRTIs do not require activation within the cell. NNRTIs are non-competitive inhibitors of mainly HIV-1 reverse transcriptase.**
- **NNRTIs were introduced between 1996-1998. On their own, they are not so potent, but in combination with a NRTI they are extremely effective.**
- **NNRTIs are metabolized by cP4503A enzymes in the liver and thus can interact with many drugs such as, astemazole, midazolam, cyclosporine, rifampin and erythromycin.**
- **Nevirapine can cause serious hepatotoxicity. Therefore, liver functions need to be monitored during therapy.**

protease inhibitors



Protease inhibitors

- *Saquinavir, ritonavir* and ***indinavir*** are well-known protease inhibitors in the treatment of HIV-infection.
- These drugs inhibit the enzymes (proteases) that split viral proteins. In this way the formation of essential polypeptides and enzymes is decreased.
- This leads to production of immature and non-functional new viruses, which are not able to infect new cells.
- All protease inhibitors cause gastrointestinal side effects. Moreover, long-term therapy can be implicated in lipodystrophy and dyslipidemia.
- All protease inhibitors are inhibitors of the CYP3A4 system and thus interact with numerous other drugs.

Currently Available Antiretroviral Agents

Agent	Class			ESO	Comments
Abacavir	NRTI	300 mg bid		Rash, hypersensitivity reaction, nausea	Do not rechallenge after hypersensitivity reaction
Amprenavir	PI	1200 mg bid	Separate dosing from didanosine or antacids by 1 hour. Avoid high-fat meals.	Rash, diarrhea, nausea	See footnote 2 for concurrent drug contraindications. Oral solution contraindicated in young children and pregnant women.
Delavirdine	NNRTI	400 mg tid	Separate dosing from didanosine or antacids by 1 hour.	Rash, liver function abnormalities	Teratogenic; see footnote 2 for concurrent drug contraindications

Agent	Class			ESO	Comments
Didanosine[3]	NRTI	150–200 mg bid, Enteric-coated: 250–400 mg qd, depending on weight	30 minutes before or 2 hours after meals	Peripheral neuropathy, pancreatitis, diarrhea, hyperuricemia	Contains antacid; avoid alcohol; avoid concurrent neuropathic drugs (eg, didanosine, zalcitabine, isoniazid)
Efavirenz	NNRTI	600 mg qd	Not to be taken with a fatty meal	Dizziness, insomnia, rash, transaminitis	Embryotoxic; see footnote 2 for concurrent drug contraindications
Enfuvirtide	Fusion inhibitor	90 mg bid	Reconstitute for subcutaneou	Local injection site reactions	Refrigeration required
Indinavir	PI	800 mg tid	1 hour before or 2 hours after a meal. Drink at least 48 oz of liquid daily. Separate dosing with didanosine by 1 hour.	Nephrolithiasis, nausea, liver function abnormalities	Store in original container, which contains dessicant; see footnote 2 for concurrent drug contraindications

Lamivudine[3]	**NRTI**	**150 mg bid or 300 mg qd, depending on weight**		**Nausea, headache, fatigue**	**Active against HBV as well as HIV-1**
Lopinavir/ritonavir	**PI/PI**	**400 mg/l00 mg bid**	**With food. Separate dosing with didanosine by 1 hour.**	**Diarrhea, abdominal pain, nausea**	**The oral solution contains alcohol; store capsules and solution in refrigerator; see footnote 2 for concurrent drug contraindications.**
Nelfinavir	**PI**	**750 mg tid or 1250 mg bid**	**With food**	**Diarrhea, nausea, flatulence**	**See footnote 2 for concurrent drug contraindications**
Nevirapine	**NNRTI**	**200 mg bid**		**Rash, hepatitis, nausea, headache**	**Dose-escalate from 200 mg qd over 14 days to decrease frequency of rash. Avoid concurrent use with ketoconazole, methadone, and oral contraceptives.**

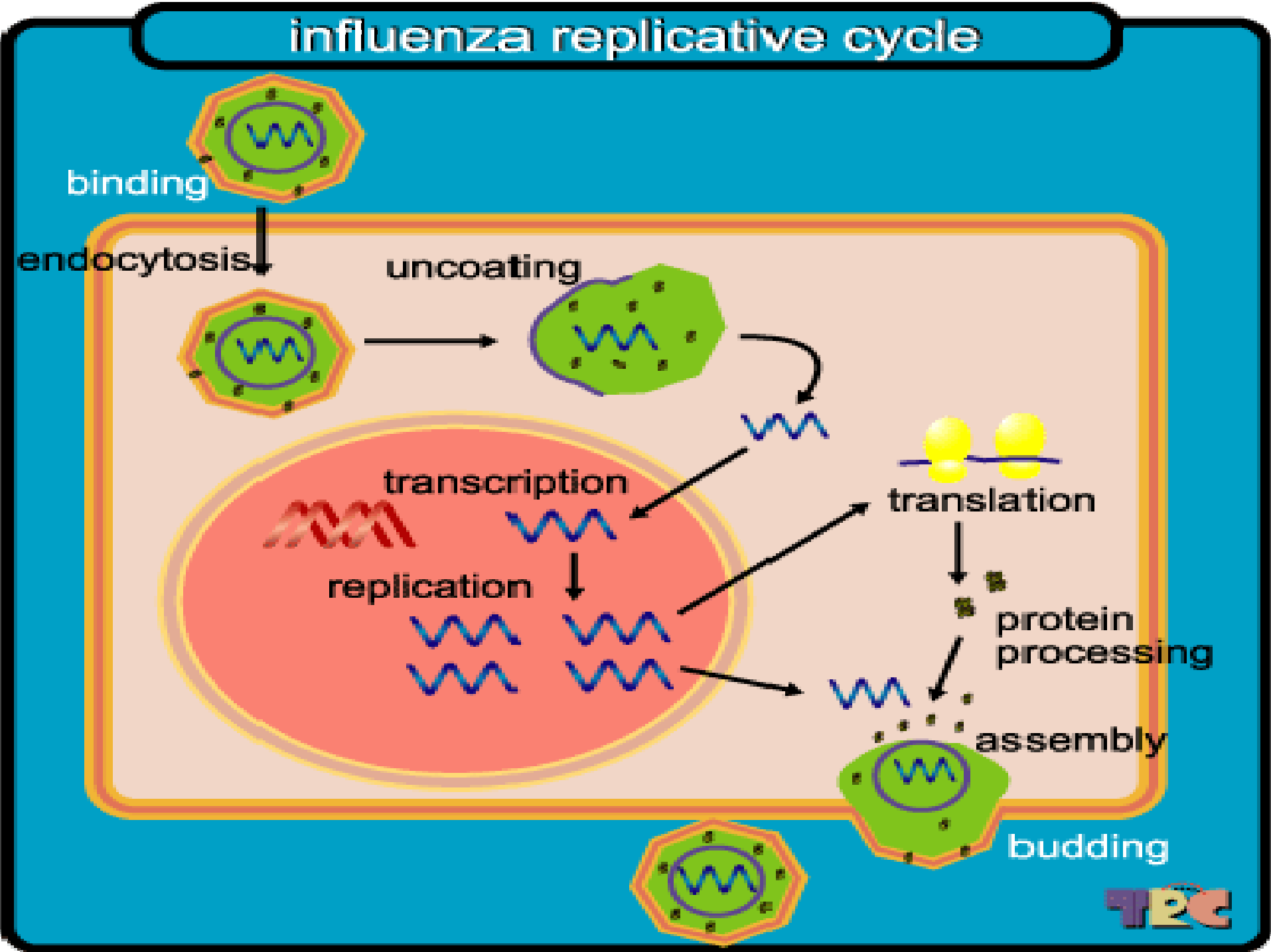
Ritonavir	**PI**	**600 mg bid**	**With food. Separate dosing with didanosine by 2 hours.**	**Nausea, diarrhea, paresthesias, hepatitis**	**Dose-escalate over 5–10 days to improve tolerance. In combination with saquinavir (400 mg bid), use 400 mg bid ritonavir. Refrigerate capsules but not oral solution. See footnote 2 for concurrent drug contraindications; avoid concurrent oral contraceptives.**
Saquinavir hard gel	**PI**	**600 mg tid or 400 mg bid with ritonavir 400 mg bid**	**Within 2 hours of a full meal**	**Nausea, diarrhea, rhinitis**	**Refrigeration recommended; see footnote 2 for concurrent drug contraindications.**
Saquinavir soft gel	**PI**	**1200 mg tid or 1800 mg bid or 1600 mg qd with ritonavir 100 mg qd**	**Within 2 hours of a full meal**	**Nausea, diarrhea, abdominal pain, dyspepsia**	**Refrigeration recommended; see footnote 2 for concurrent drug contraindications.**

Stavudine[3]	**NRTI**	**30–40 mg bid, depending on weight**		**Peripheral neuropathy, stomatitis**	**Avoid concurrent neuropathic drugs (eg, didanosine, zalcitabine, isoniazid); avoid concurrent use with zidovudine**
Tenofovir[4]	**Nucleotide inhibitor**	**300 mg qd**	**With a meal. Separate dosing with didanosine by 1–2 hours**	**Nausea, vomiting, diarrhea, flatulence**	
Zalcitabine[3]	**NRTI**	**0.75 mg tid**	**Avoid administration with antacids or food**	**Peripheral neuropathy; oral ulcerations**	**Avoid concurrent neuropathic drugs (eg, didanosine, stavudine, isoniazid)**
Zidovudine[3]	**NRTI**	**200 mg tid or 300 mg bid**		**Anemia, neutropenia, nausea, insomnia**	**Avoid concurrent myelosuppressive drugs (eg, ganciclovir, ribavirin)**

- The following drugs are contraindicated as concurrent medications: astemizole, terfenadine, dihydroergotamine, cisapride, pimozide, midazolam, triazolam, flecainide, propafenone, rifampin, lovastatin, simvastatin, St. John's wort.

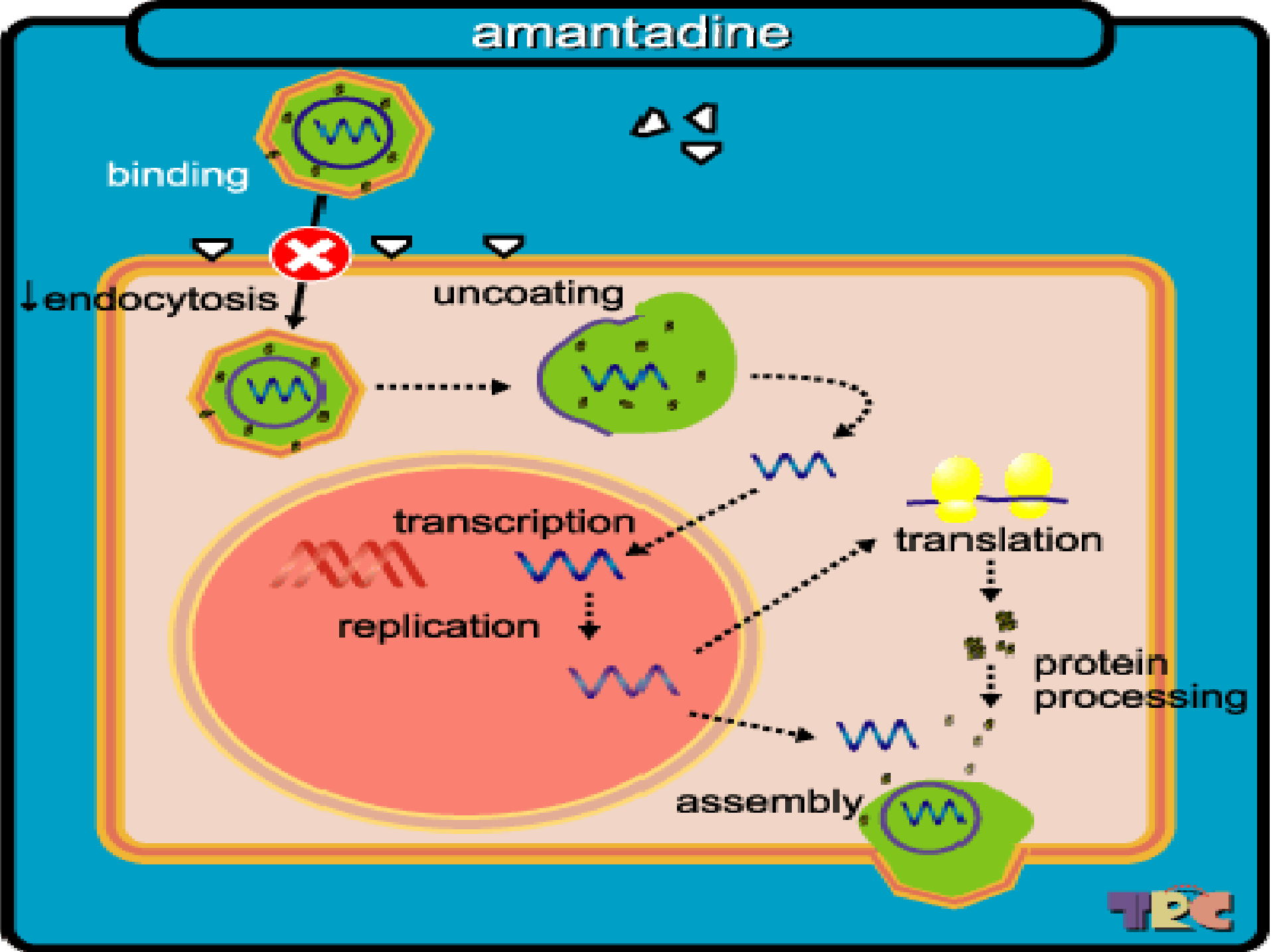
Drug Interactions Pertaining to Two-Drug Antiretroviral Combinations.

Agent	Drugs That Will Increase Its Serum Levels	Drugs That Will Decrease Its Serum Levels
Amprenavir	Abacavir, delavirdine, indinavir, lopinavir, ritonavir, zidovudine	Didanosine, efavirenz, nevirapine, saquinavir
Delavirdine	Saquinavir	Didanosine, nelfinavir
Didanosine	Tenofovir	Delavirdine
Efavirenz	Ritonavir	
Indinavir	Delavirdine, lopinavir, nelfinavir, zidovudine	Amprenavir, delavirdine, efavirenz, nevirapine, ritonavir
Lamivudine	Nelfinavir	
Lopinavir	Delavirdine, ritonavir	
Nelfinavir	Delavirdine, efavirenz, ritonavir, saquinavir	
Ritonavir	Delavirdine, efavirenz	Didanosine, indinavir, zidovudine
Saquinavir	Delavirdine, lopinavir, nelfinavir, ritonavir	Efavirenz, nevirapine


influenza replicative cycle
binding
endocytosis
uncoating
transcription
replication
translation
protein
processing
assembly
budding

Influenza virus

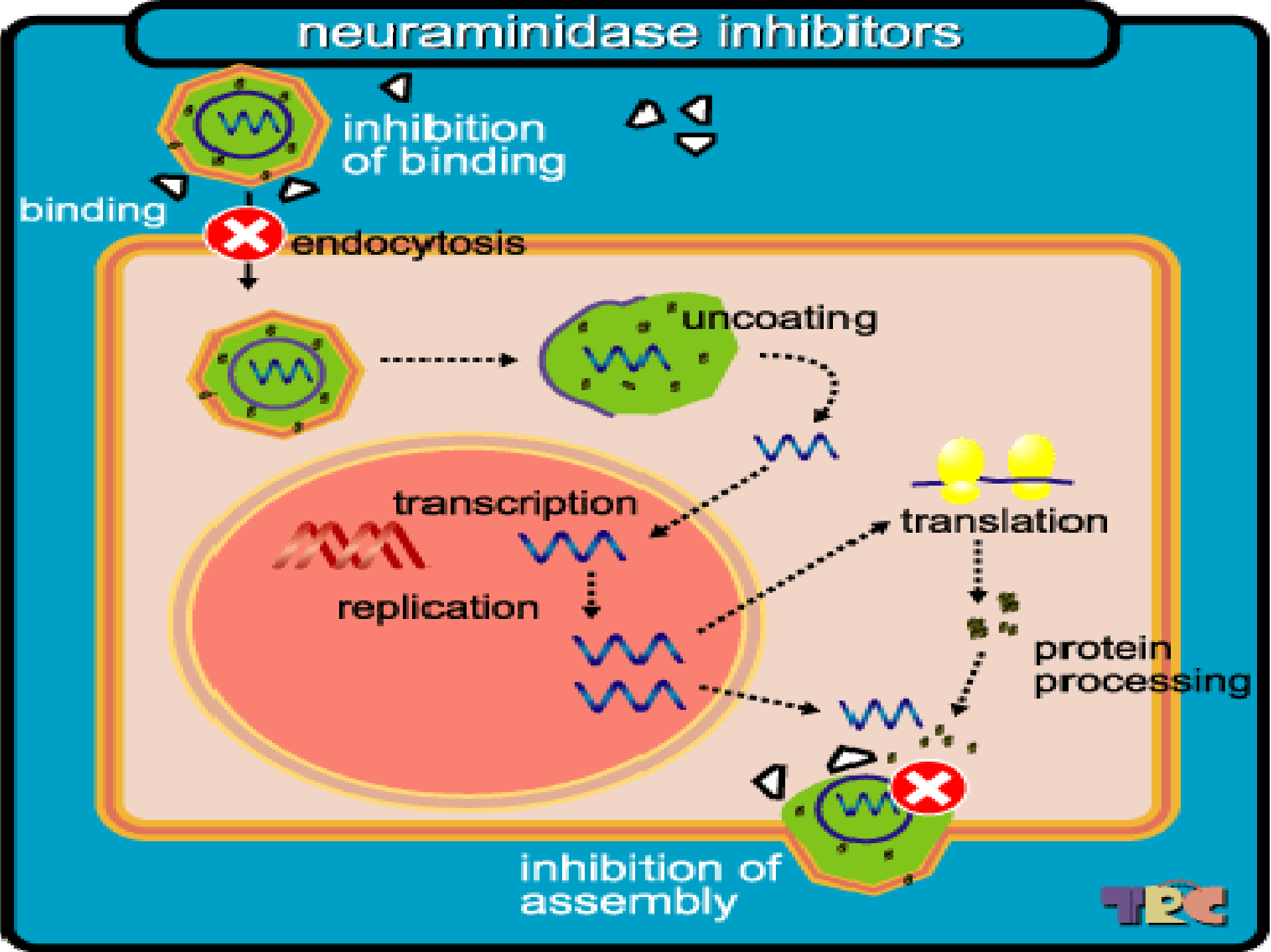
- The influenza viruses are endocytosed in the host cell and are uncoated in the cytoplasm.
- Transcription and replication happens in the host cell nucleus.
- After the assembly of the viral RNA and protein in the cytoplasm, the new virus buds from the host cell plasma membrane.


amantadine
binding
endocytosis
uncoating
transcription
replication
translation
protein
processing
assembly

Amantadine

- ***Amantadine***. Their exact mechanism of action as antiviral drug is unknown.
- Amantadine inhibits an early step in viral replication: penetration of the virus into the host cell.
- It also prevents the uncoating of the virus, thereby inhibiting the release of viral genetic material.
- Secondly, amantadine might also interfere with the last step in the replication cycle, thereby inhibiting viral assembly.
- Amantadine is well absorbed orally and has a large volume of distribution. The drug is excreted largely unchanged in urine. Common side effects include gastrointestinal problems and CNS complaints.
- High doses can be neurotoxic and result in seizures or coma.

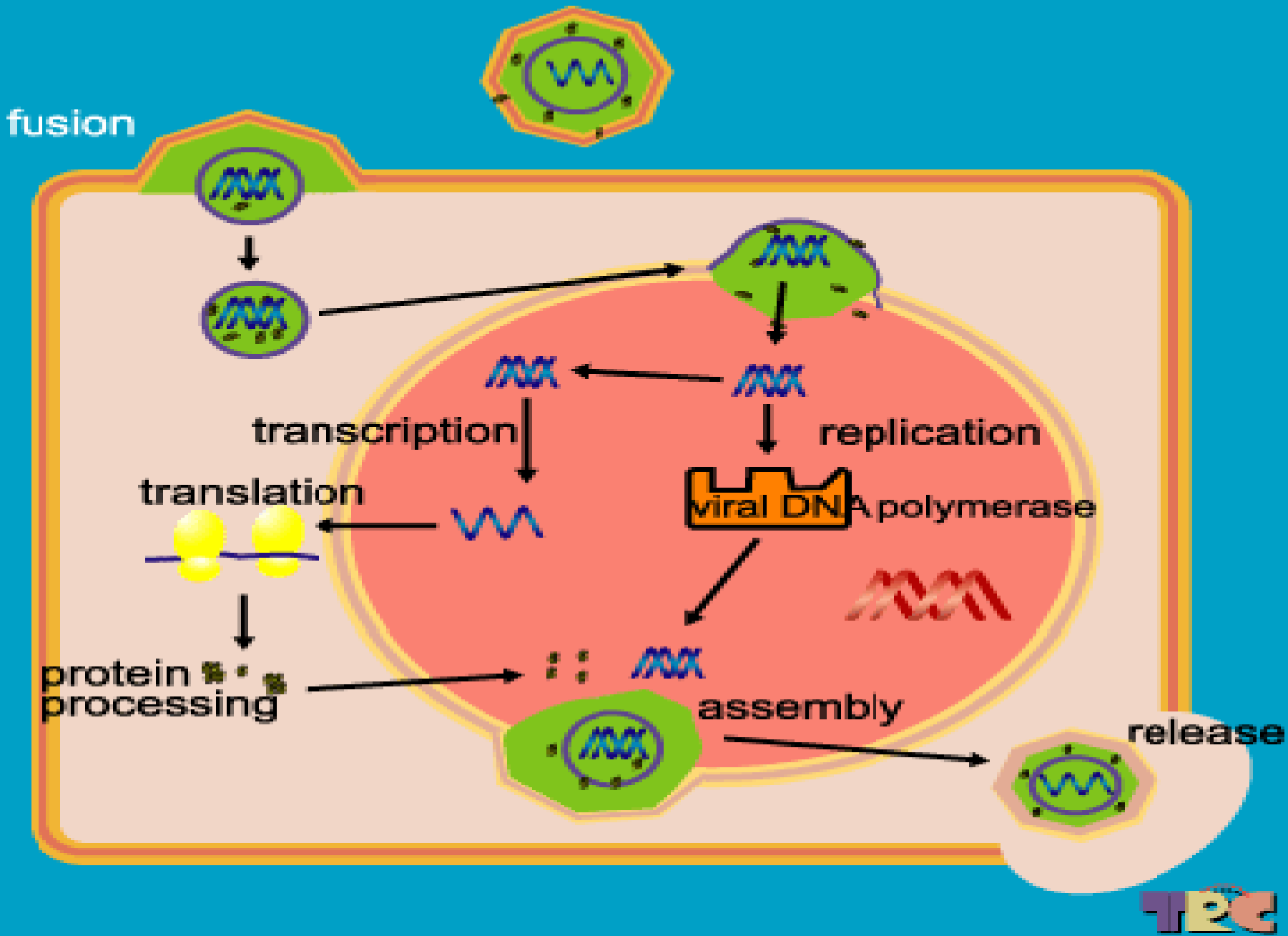
neuraminidase inhibitors



Neuraminidase inhibitors

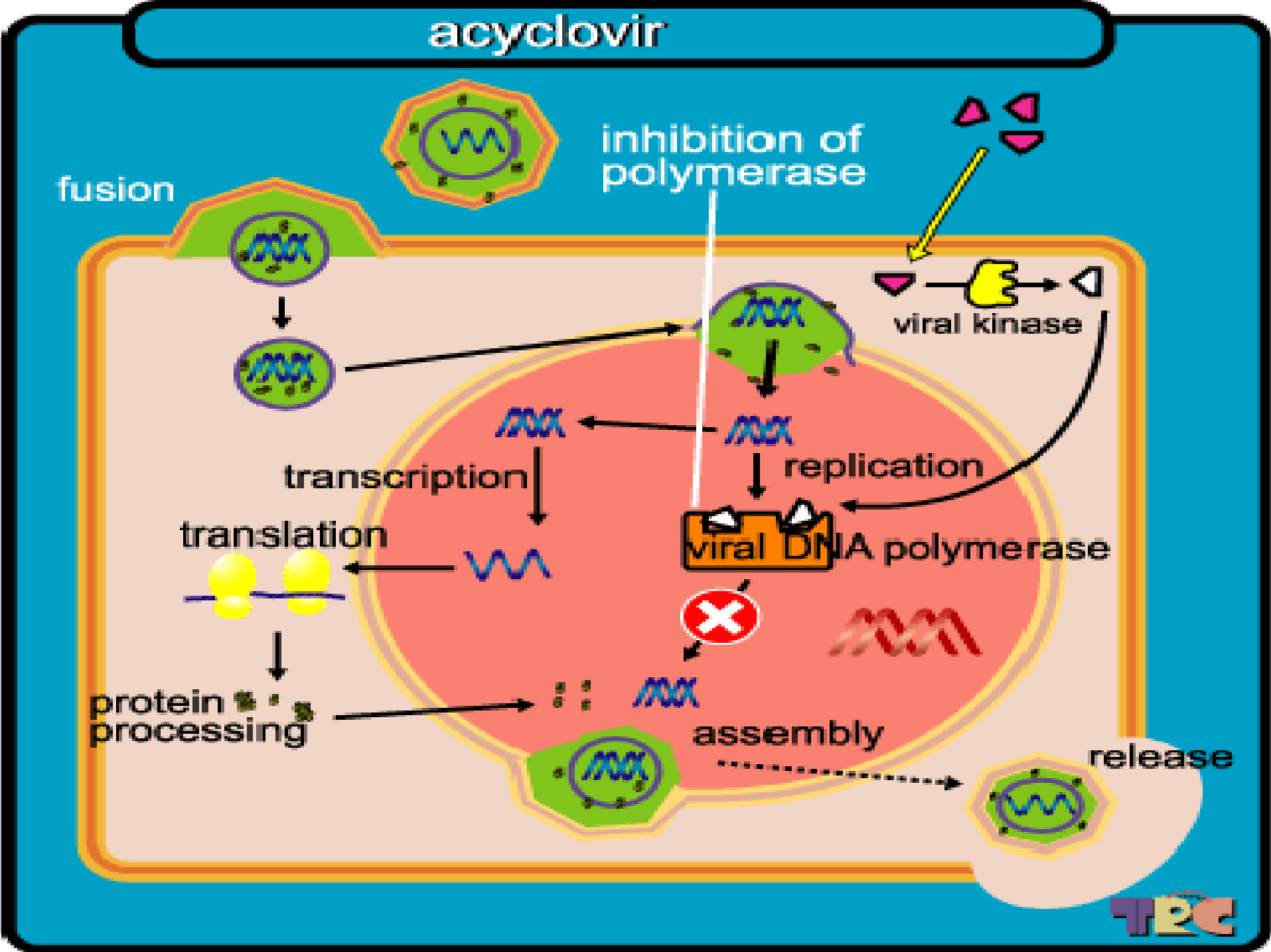
- ***Oseltamivir*** is a relatively new drug. It is a prodrug of a selective inhibitor of neuraminidase, an enzyme and glycoprotein at the surface of influenza virus.
- Neuraminidase stimulates the penetration of the virus and facilitates the release of newly formed viruses. Oseltamivir thus causes viral aggregation at the cell surface and reduces viral replication.
- The drug is registered for the prevention and treatment of influenza A and B virus infections. Oseltamivir is generally well-tolerated.

herpes replicative cycle



Herpes virus

- Herpes viruses have an envelope and carry DNA in the capsid.
- Their replication begins with recognition by the host cell and is followed by fusion of the envelope with the cell membrane and release of the nucleocapsid.
- Inside the host cell, the nucleocapsid fuses with the nuclear membrane. Inside the nucleus the viral DNA is transcribed and replicated via viral DNA polymerase.
- In the meantime viral proteins are synthesized and assembly occurs in the nucleus. The nuclear membrane is used as envelope. The new viruses are released via exocytosis or by lysis of the host cell


acyclovir
fusion
inhibition of polymerase
viral kinase
transcription
replication
translation
viral DNA polymerase
protein processing
assembly
release

Acyclovir

- ***Acyclovir*** and ***valaciclovir*** belong to the group of nucleoside inhibitors of herpes viruses.
- Acyclovir is converted in the cell into active acyclovir triphosphate by the viral enzyme thymidine kinase. The triphosphate form competitively inhibits the viral DNA polymerase.
- This leads to a blockade of the viral DNA synthesis and thus of the viral replication.
- The related drugs ***ganciclovir*** and ***valganciclovir*** are drug of choice in cytomegalovirus infection.

Half-life: t1/2= 2,4 h

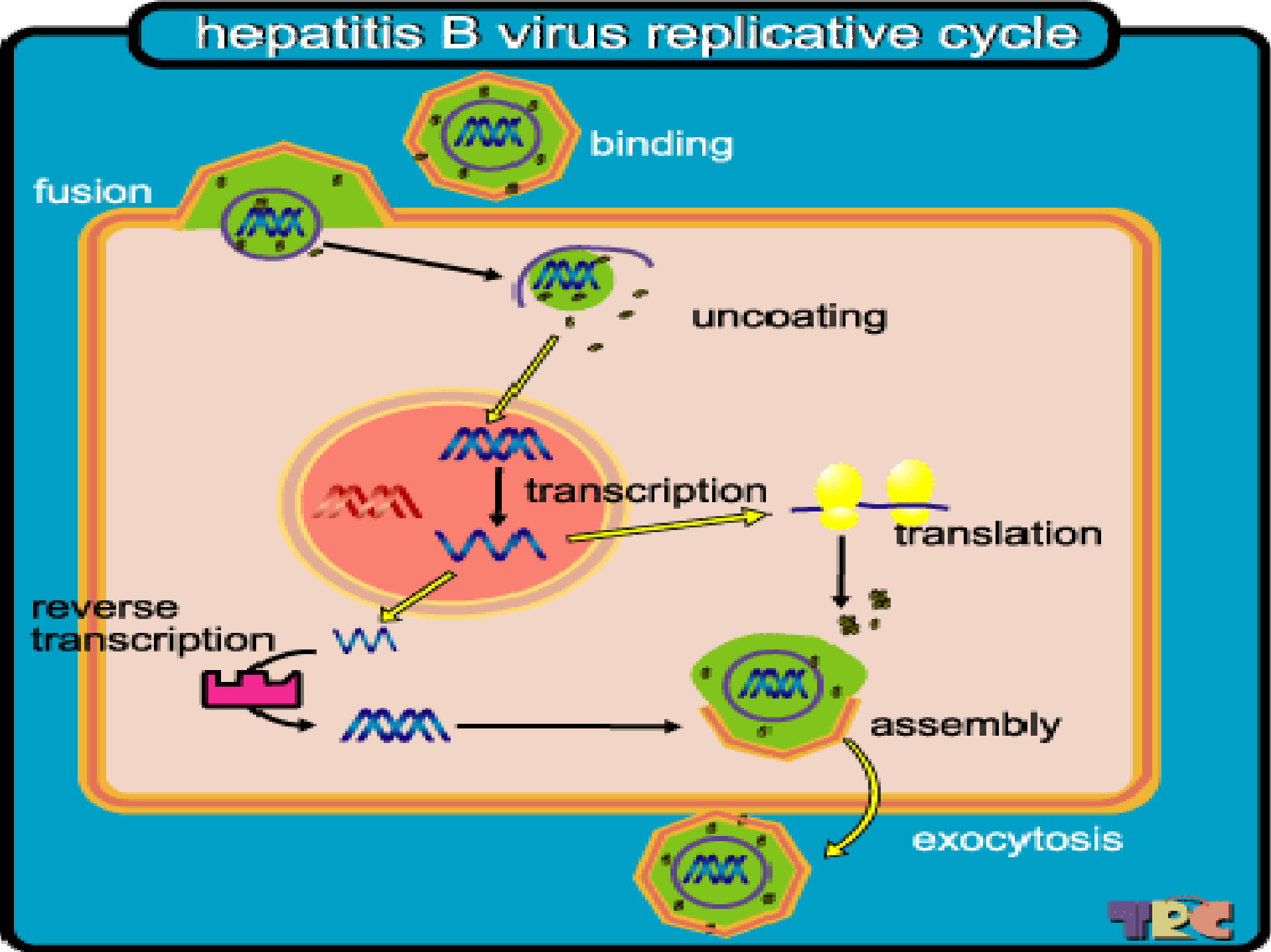
Agents to Treat or Prevent Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) Infections.

Agent	Route	Use	Recommended Adult Dosage and Regimen
Acyclovir	Oral	First episode genital herpes	400 mg tid or 200 mg five times daily
		Recurrent genital herpes	400 mg tid or 200 mg five times daily or 800 mg bid
		Genital herpes suppression	400 mg bid
		Herpes proctitis	400 mg five times daily
		Mucocutaneous herpes in the immunocompromised host	400 mg five times daily
		Varicella	20 mg/kg (maximum 800 mg) four times daily
		Zoster	800 mg five times daily
	IV	Severe HSV infection	5 mg/kg q8h
		Herpes encephalitis	10–15 mg/kg q8h
		Neonatal HSV infection	20 mg/kg q8h
		Varicella or zoster in the	10 mg/kg q8h

Agents to Treat or Prevent Herpes Simplex Virus (HSV) and Varicella-Zoster Virus (VZV) Infections.

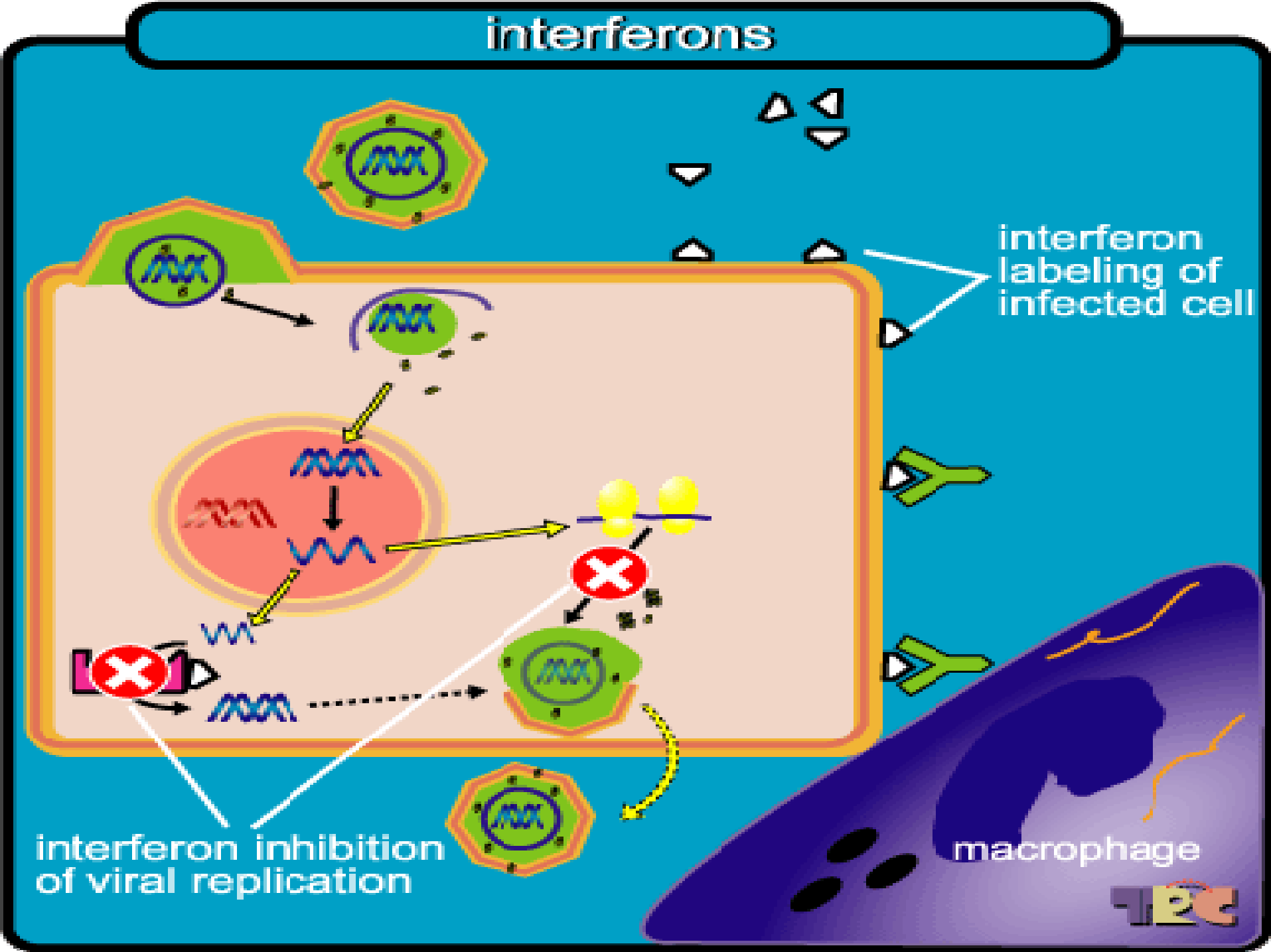
Agent	Route	Use	Recommended Adult Dosage and Regimen
Famciclovir[1]	Oral	First episode genital herpes	250 mg tid
		Recurrent genital herpes	125 mg bid
		Genital herpes suppression	250 mg bid
		Zoster	500 mg tid
Valacyclovir[1]	Oral	First episode genital herpes	1 g bid
		Recurrent genital herpes	500 mg bid
		Genital herpes suppression	500 mg daily or twice daily
		Zoster	1 g tid
Foscarnet[1]	Intravenous	Acyclovir-resistant HSV and VZV infections	40 mg/kg q8-12h
Penciclovir	Topical	Recurrent herpes labialis	Thin film covering lesion every 2 hours
Trifluridine	Topical	Herpes keratitis	1 drop every 2 hours
		Acyclovir-resistant HSV infection	Thin film covering lesion five times daily

hepatitis B virus replicative cycle



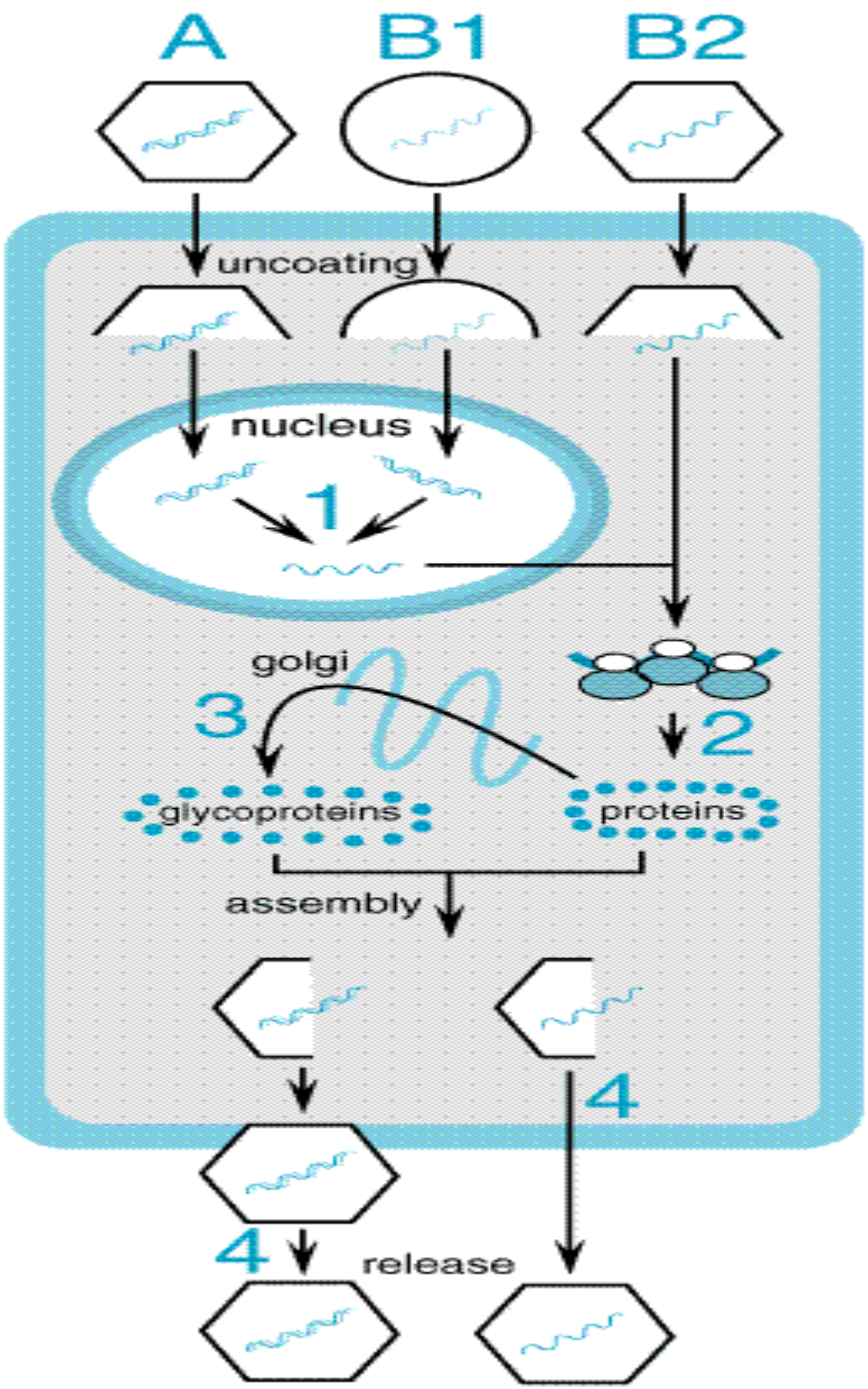
Hepatitis B virus

- After entry into the hepatocyte, the DNA of the hepatitis virus is brought to the nucleus.
- There the viral DNA is transcribed and the resulting mRNA is transported to the cytoplasm. Here the mRNA is either reverse transcribed into viral DNA or translated into viral proteins.
- The viral DNA and proteins are assembled and enveloped before exocytosis.


interferons
interferon labeling of infected cell
interferon inhibition of viral replication
macrophage

Interferons

- *Interferons* (***IFN-a 2a*** and ***IFN-a 2b***) are cytokines that possess antiviral and immunomodulating actions.
- Interferons “mark” infected cells by binding to the cell membrane of virus-infected cells, initiate complex actions inside the cell that prevent viral replication and activate the immune system.
- Interferons are administered via intramuscular, intravenous or subcutaneous injection.
- Elimination from the blood relates to distribution, cellular uptake and catabolism in liver and kidney.
- Adverse effects of interferons are acute influenza-like symptoms. In higher doses, interferons can cause myelosuppression.



Viruses

A. DNA

B. RNA

1. orthomyxoviruses and retroviruses
2. picornaviruses and most RNA viruses

IFN Effects

1. transcription inhibition

activates Mx protein
blocks mRNA synthesis

2. translation inhibition

activates methylase —>
blocks mRNA cap methylation

activates 2'5' oligoadenylate synthetase —> 2'5'A —> inhibits mRNA splicing and activates RNase L —> cleaves viral RNA

activates protein kinase P1 —> blocks eIF-2α function —> inhibits initiation of mRNA translation

activates phosphodiesterase —> blocks tRNA function

3. protein processing inhibition

glycosyltransferase —> blocks protein glycosylation

4. virus maturation inhibition

glycosyltransferase —>blocks glycoprotein maturation

causes membrane changes —> blocks budding