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Antiviral and Antifungal

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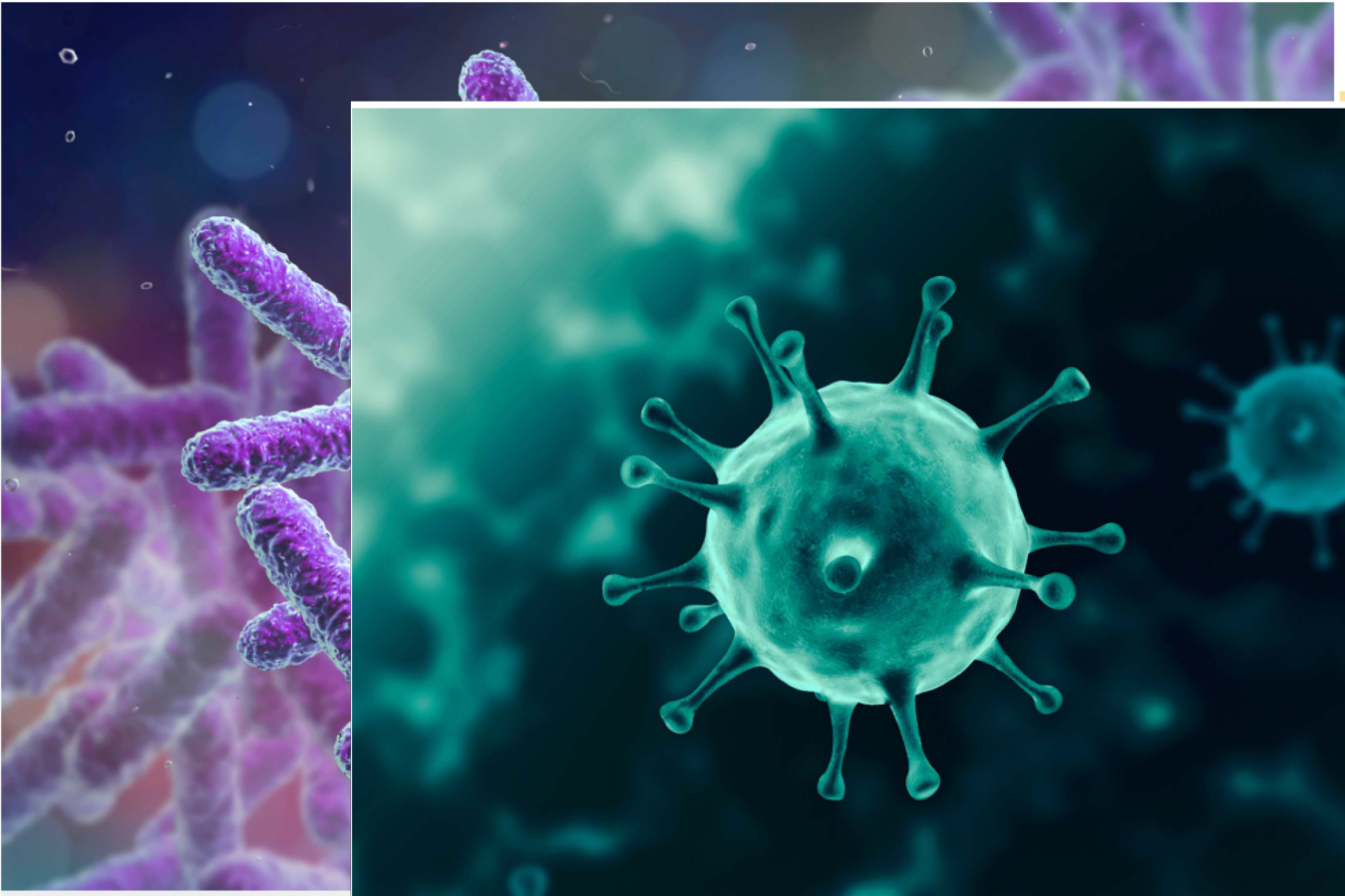
What's the difference between bacteria and viruses?



Bacteria

Viruses are a non-living collection of molecules that need a host to survive.

Bacteria reproduce mainly by binary fission

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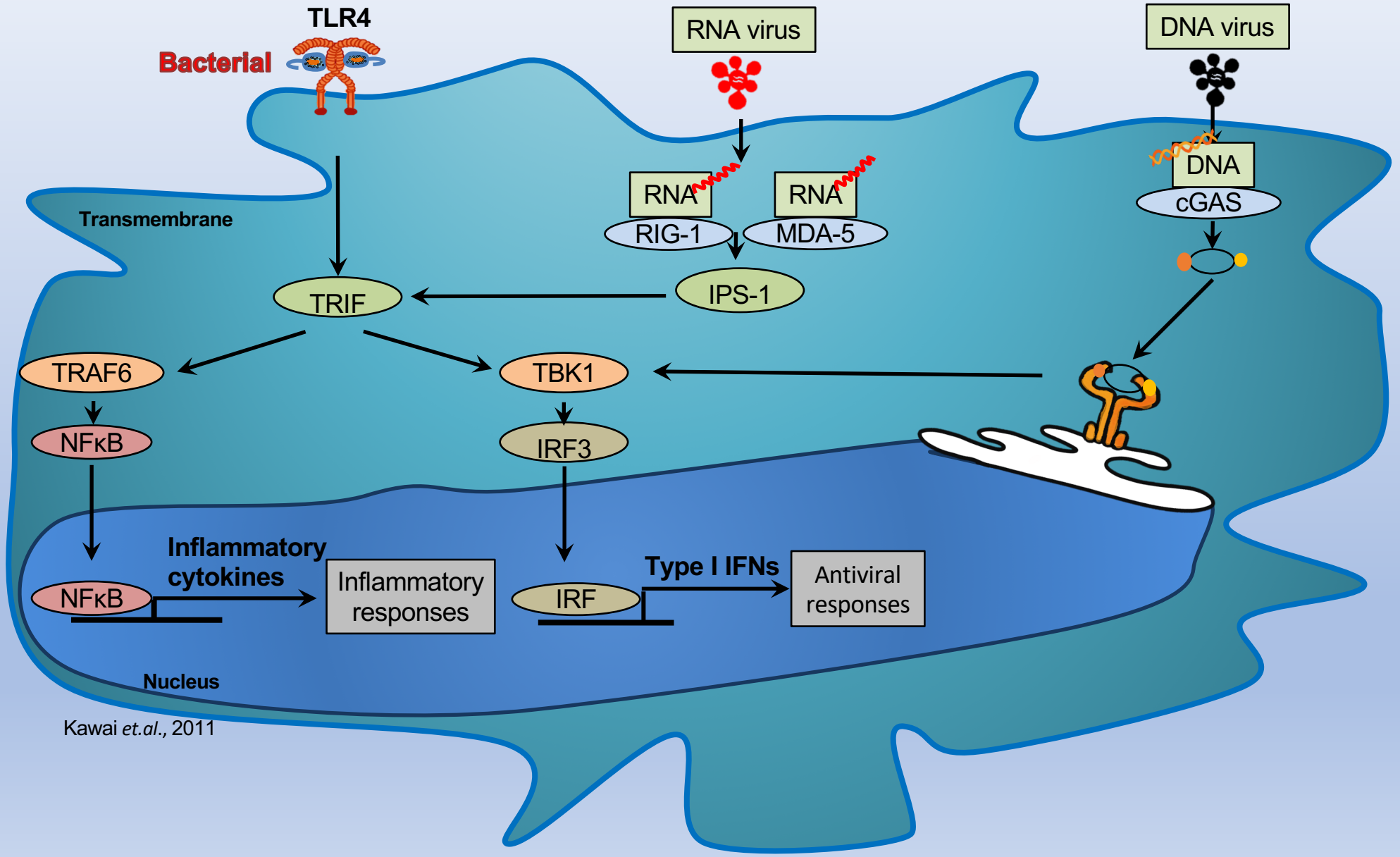
Innate immune signaling



Kawai *et.al.*, 2011

Viruses

A virus is a small parasite that cannot reproduce by itself.
Once it infects a susceptible cell, however, a virus can direct the cell machinery to produce more viruses.

(Lodish H, Berk A, Zipursky SL, et al. 2000)

A virus is tiny, infectious particle that reproduce only by infecting a host cells.
Basically package of nucleic acid and protein

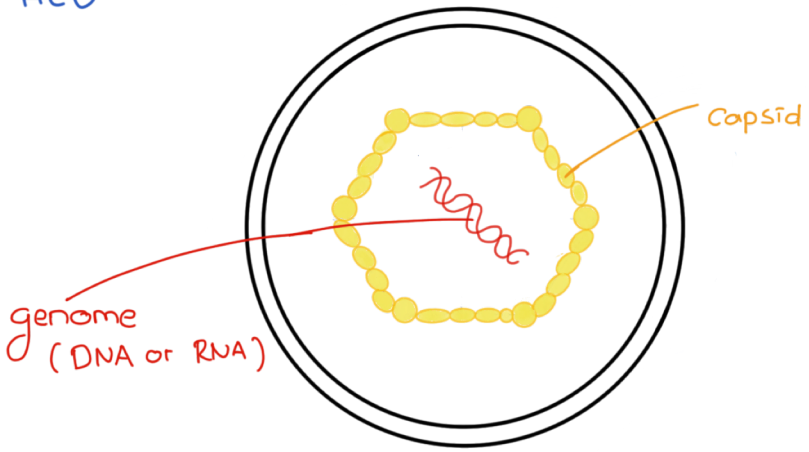
(Raven and Johnson, 2002)

Viruses consist of :

- Genetic material, a nucleic acid (DNA or RNA, may be single-or double- stranded)
- Nucleocapsid, a protective protein shell
- Envelope, a layer of membrane (some viruses has, but not all viruses)

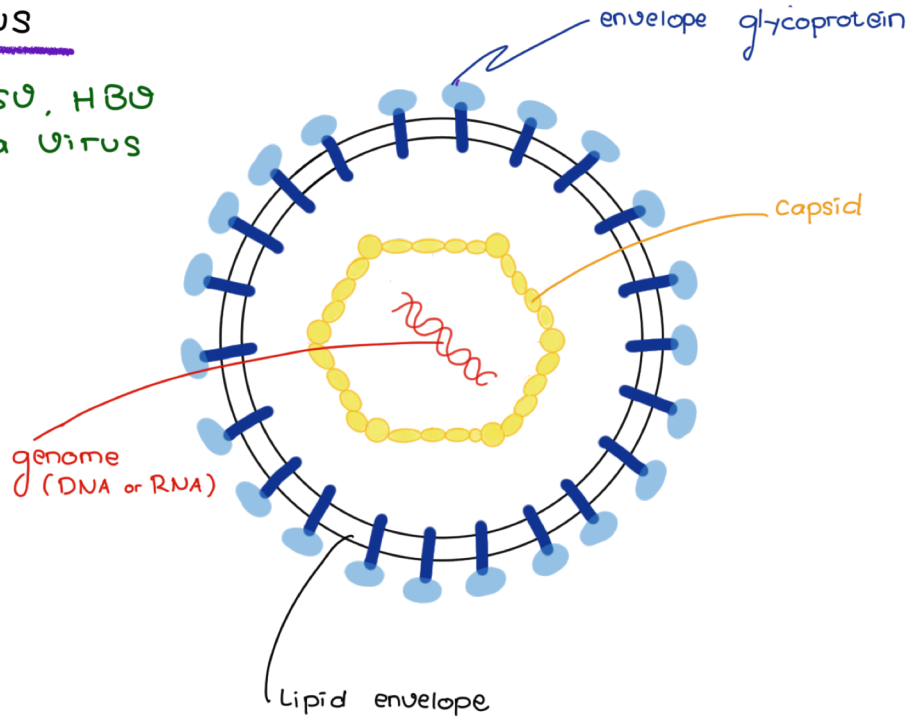
Non- Envelope Virus

→ Norovirus , Parvovirus
HAV , HEV



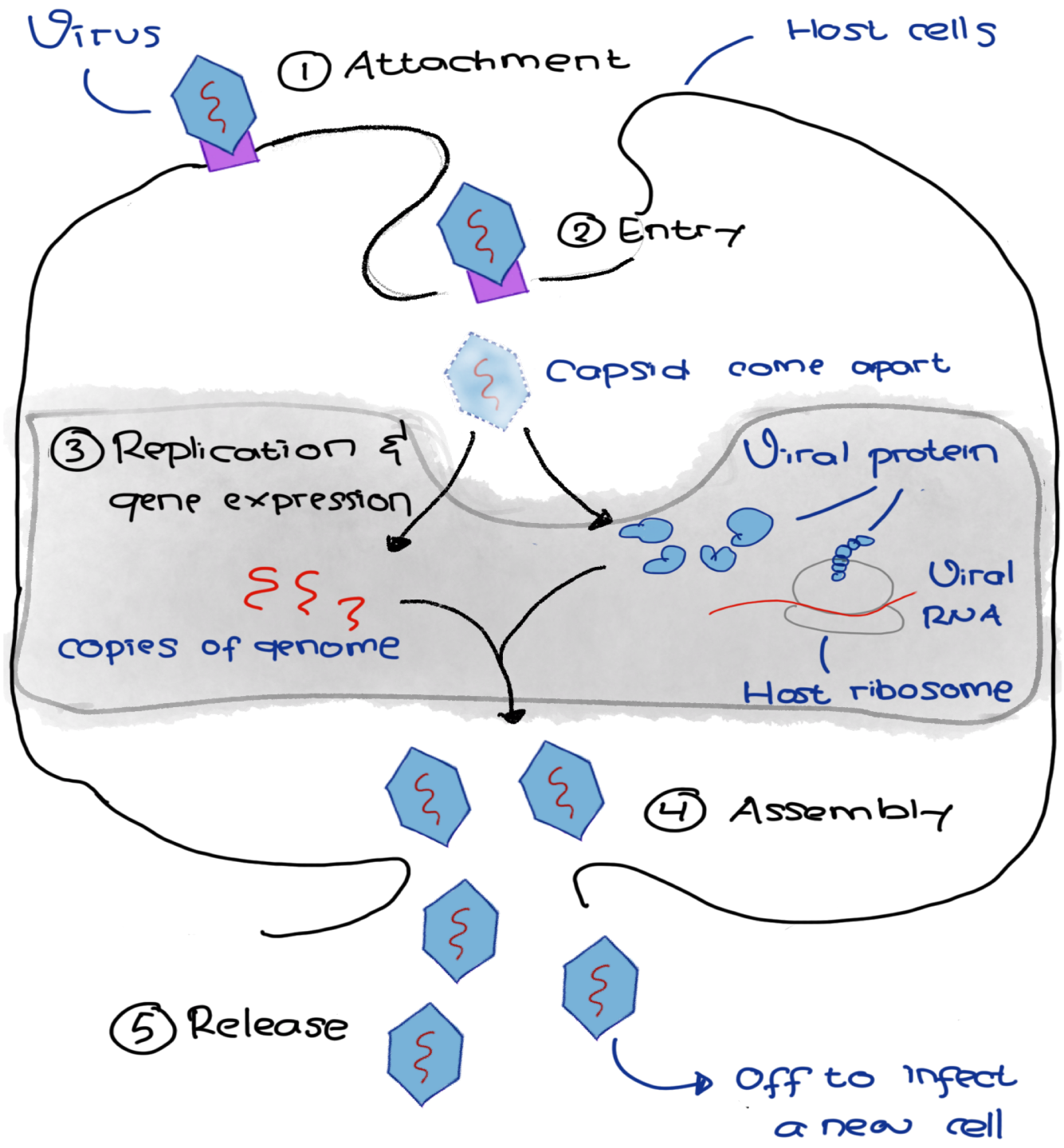
Envelope Virus

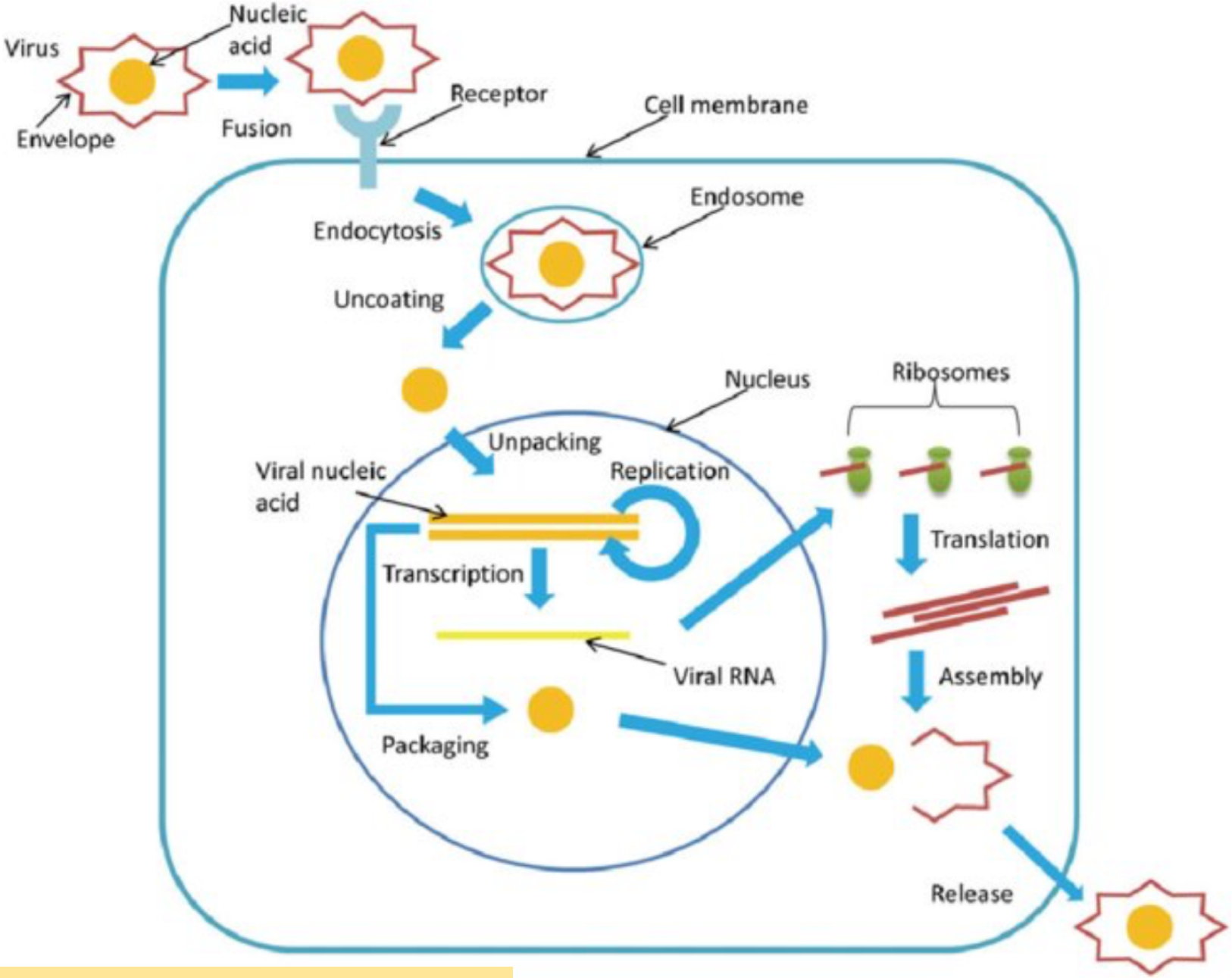
→ HIV, HSV, HBV
Influenza virus



General diagram of a virus lifecycle

1. Attachment
2. Entry
3. Replication and gene expression
4. Assembly
5. Release





Qureshi, A., etal., *Reviews in medical virology*, *28*(4)

Diseases due to VIRUSES

- **In humans** :

- Smallpox, chickenpox, herpes,
- Common cold, influenza,
- AIDS
- Cancer

Virus	Genus, Family	Host	Transmission	Disease
Hepatitis A virus	Hepatovirus, picornaviridae	Human	Fecal-oral	Hepatitis
Hepatitis B virus	Orthohepadnavirus, Hepadnaviridae	Human, Chimpanzees	Sexual contact, blood	Hepatitis
Hepatitis C virus	Hepacivirus, Flaviviridae	Human	Sexual, blood	Hepatitis
Hepatitis E virus	Hepevirus, Unassigned	Human, pig, monkeys, some rodents, chicken	Zoonosis, food	Hepatitis
Hepatitis delta virus	Deltavirus, Unassigned	Human	Sexual contact, blood	Hepatitis
Horsepox virus	Orthopoxvirus, Poxviridae	Human, horses	Zoonosis, contact	None
Human adenovirus	Mastadenovirus, Adenoviridae	Human	Respiratory, fecal-oral	Respiratory
Human astrovirus	Mamastrovirus, Astroviridae	Human	Fecal-oral	Gastroenteritis
Human coronavirus	Alphacoronavirus, Coronaviridae	Human	Respiratory	Respiratory
Human cytomegalovirus	Cytomegalovirus, Herpesviridae	Human	Contact, urine, saliva	Mononucleosis, pneumonia
Human enterovirus 68, 70	Enterovirus, Picornaviridae	Human	Fecal-oral	Diarrhea, neurological disorder
Human herpesvirus 1	Simplexvirus, Herpesviridae	Human	Sexual contact, saliva	Skin lesions
Human herpesvirus 2	Simplexvirus, Herpesviridae	Human	Sexual contact, saliva	Skin lesions
Human herpesvirus 6	Roseolovirus, Herpesviridae	Human	Respiratory, contact	Skin lesions
Human herpesvirus 7	Roseolovirus, Herpesviridae	Human	Respiratory, contact	Skin lesions
Human herpesvirus 8	Rhadinovirus, Herpesviridae	Human	Sexual contact, saliva	Skin lymphoma
Human immunodeficiency virus	Lentivirus, Retroviridae	Human	Sexual contact, blood	AIDS

https://viralzone.expasy.org/678

- The structure of each virus differs
- Specific therapy is often **unsuccessful** because of periodic changes in the antigenic proteins of the virus (antigenic proteins provoke an immune response in the host).
- Treatment / agent of virus must be able to inhibit the virus without seriously affecting the host cells.
- An antiviral agent must act at one of five basic steps in the viral replication cycle in order to inhibit the virus

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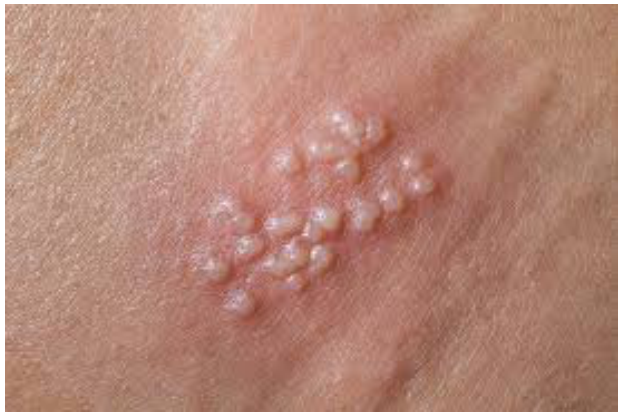
Select Groups Of Antiviral Drugs

Human Herpes Virus

Herpes-virus

- Herpesvirus is the DNA-containing virus

that causes such diseases as
- genital herpes,
- chickenpox
- retinitis, and
- Infectious mononucleosis.



Human Herpesviruses (HHV)

Taxonomic name	Common name	Viral sub-family
Human herpesvirus 1	Herpes simplex viruses 1 (HSV-1)	Alpha
Human herpesvirus 2	Herpes simplex viruses 2 (HSV-2)	Alpha
Human herpesvirus 3	Varicella-zoster virus (VZV)	Alpha
Human herpesvirus 4	Epstein-Barr virus (EBV)	Gamma
Human herpesvirus 5	Human cytomegalovirus (CMV)	Beta
Human herpesvirus 6	HHV-6	Beta
Human herpesvirus 7	HHV-7	Beta
Human herpesvirus 8	Kaposis sarcoma-associated herpesvirus	Gamma

→ Oral herpes

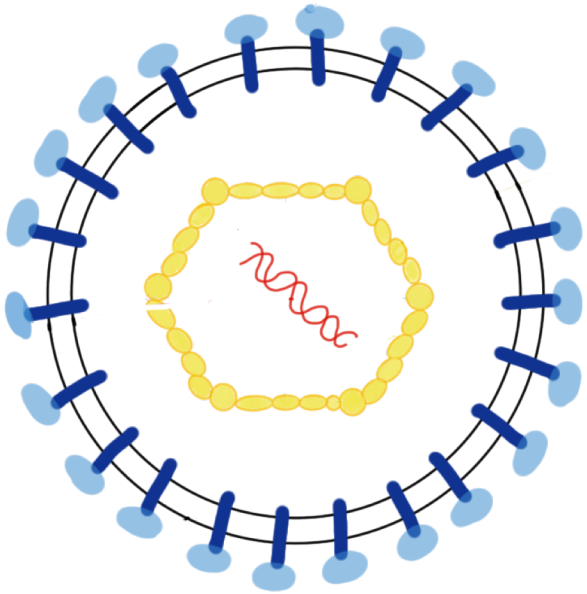
→ Genital herpes

Alpha
- Short reproductive cycle
- Latent in Sensory neurons
- Painful skin disease

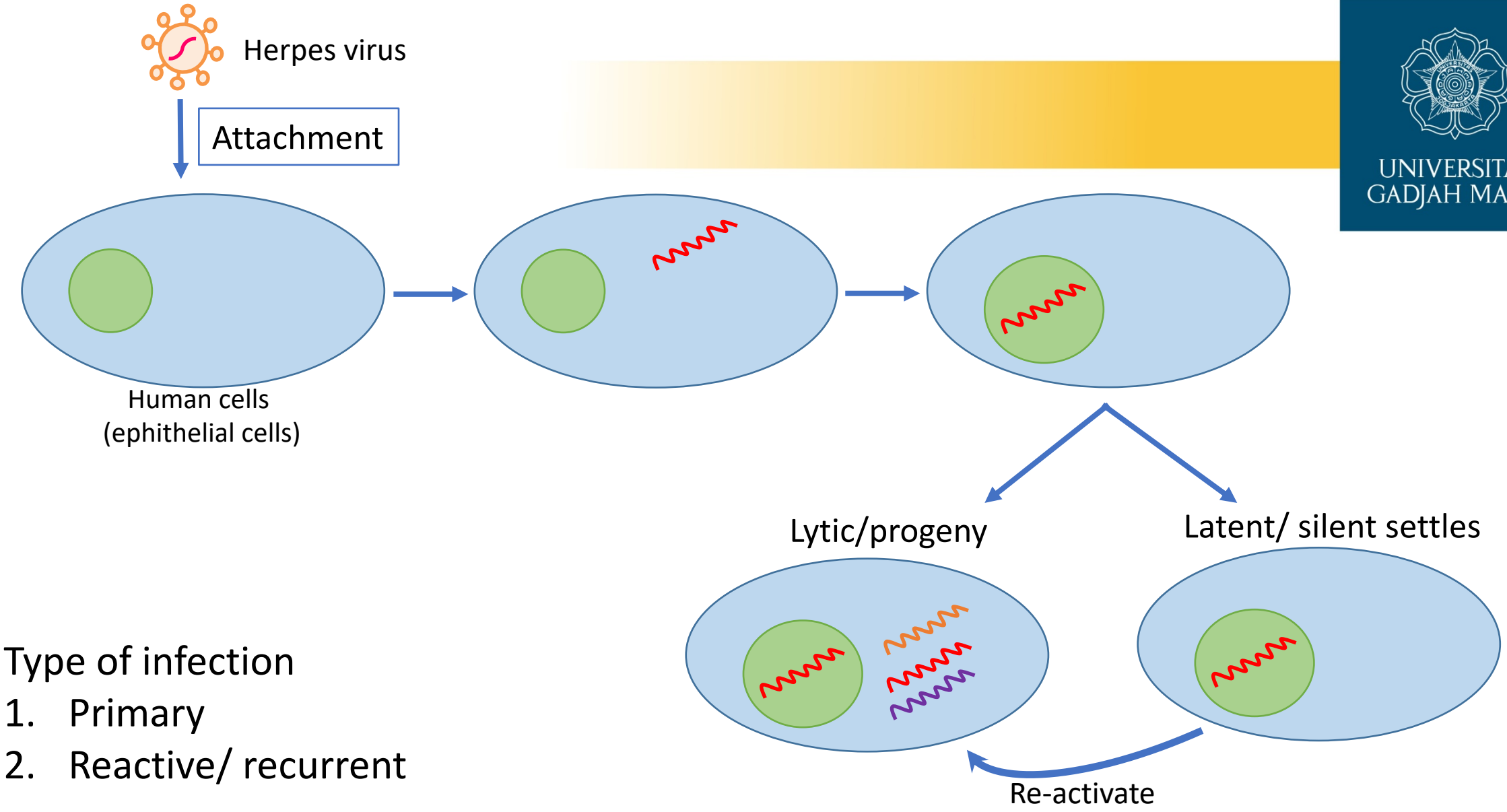
Beta
- Long reproductive cycle
- Latent in WBC

Gamma
- Latent in Lymphocytes
- Associated with cancer

Structure HHV

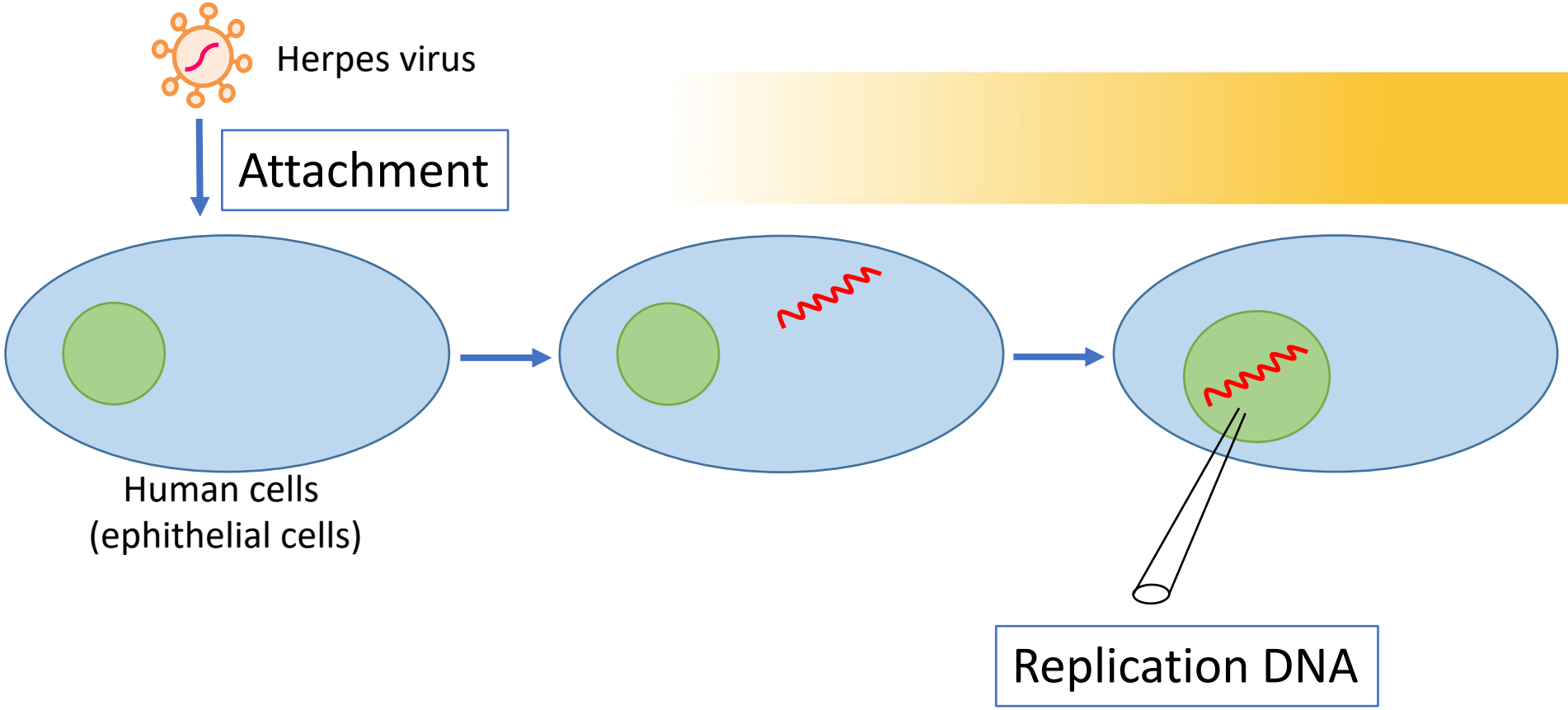


- Consist of :
- dsDNA
- Capsid
- Tegument
- Envelope
- Glycoprotein



Type of infection

1. Primary
2. Reactive/ recurrent



Require enzymes :

1. DNA polymerase α (DNA pol α)
2. RNA polymerase

Murakami et al., 1986; Luczkowiak et al., 2019

Replication DNA

1. **DNA polymerase α (Pol α-DNA primase complex)** :

Primase catalyzes the synthesis of short RNA , called the RNA primer (platform for DNA synthesis).

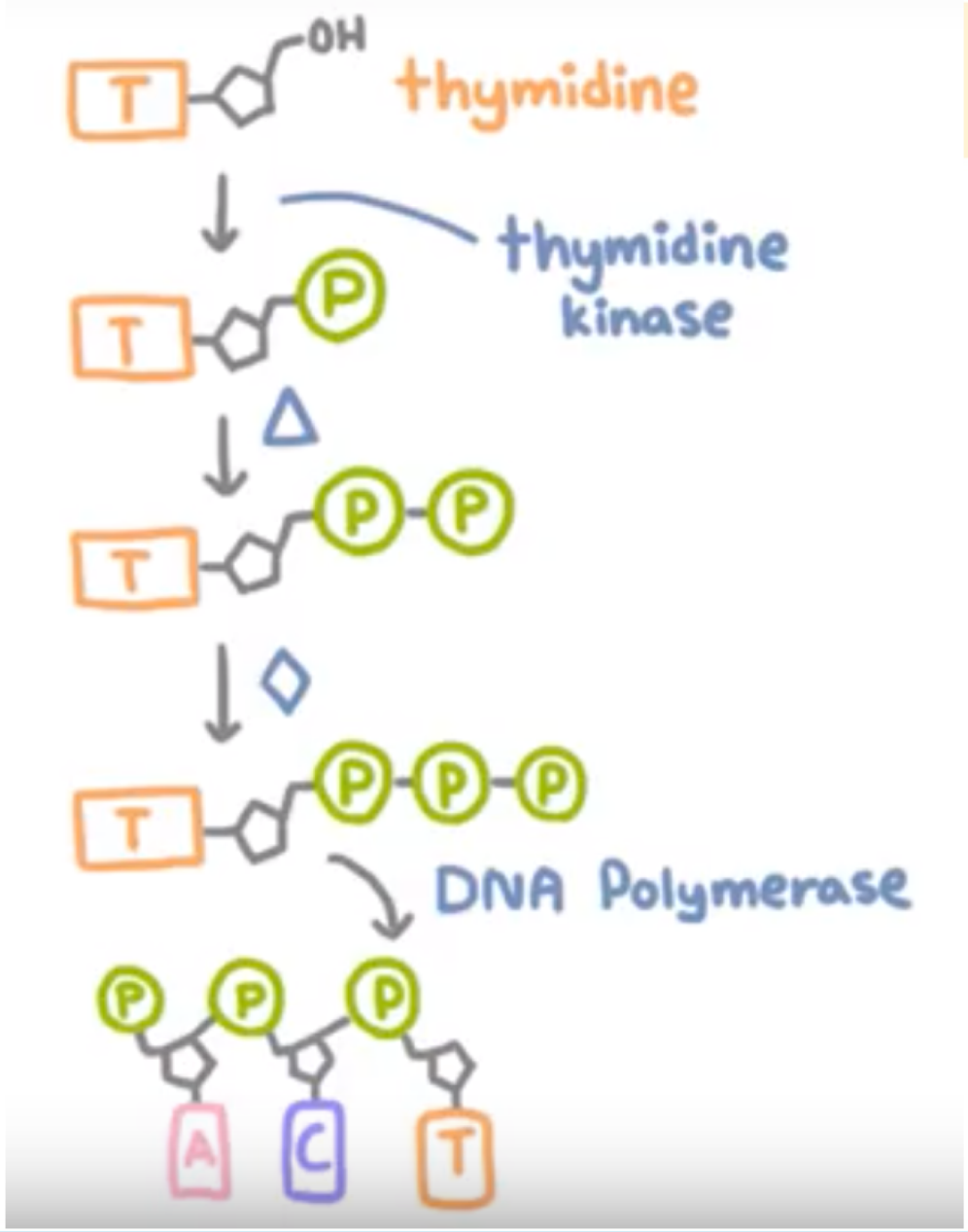
Along the DNA template, primase intersperses RNA primers that DNA polymerase uses to synthesize DNA from in the 5′→3′ direction

2. **RNA polymerase**

is an enzyme that produces RNA and catalyzes the initiation and elongation of RNA chains from a DNA template.

RNA is created using a process known as transcription.

Mene´ndez-Arias et al., 2017

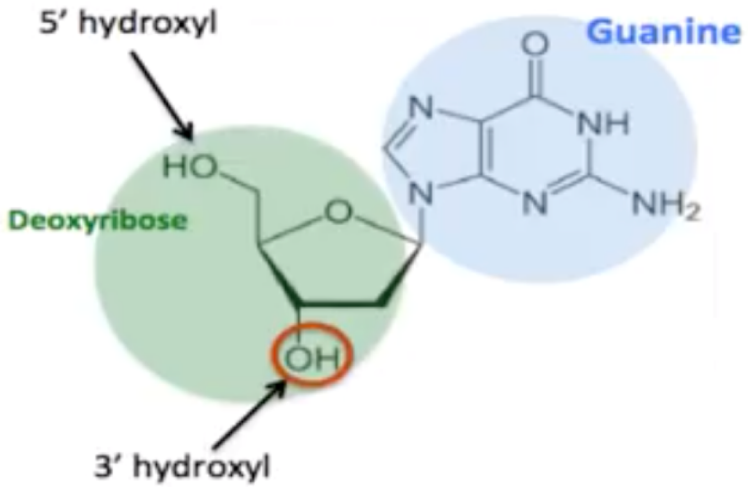


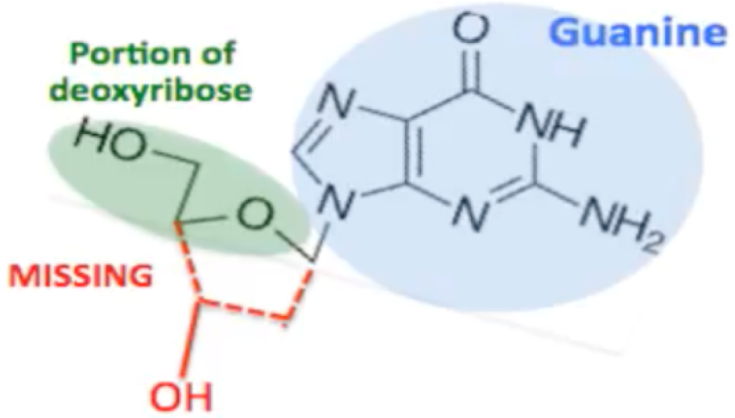
Viruses have their own

DNA Polymerase and
Kinases (to phosphorylate Thymidine into Thymidine monophosphate)

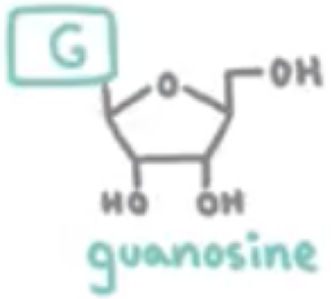
Acyclovir

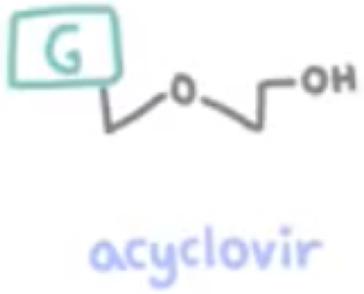
Acyclovir is a guanosine analogue



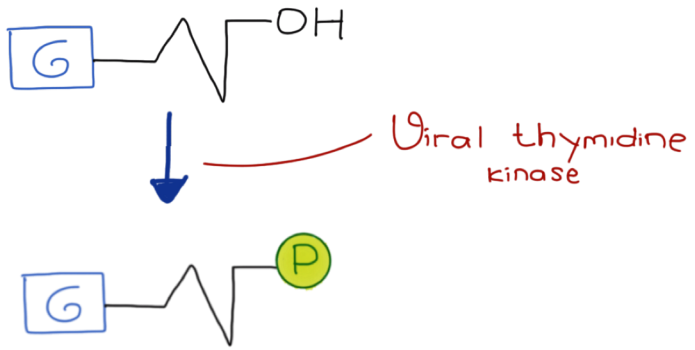


Acyclovir missing the cyclic group





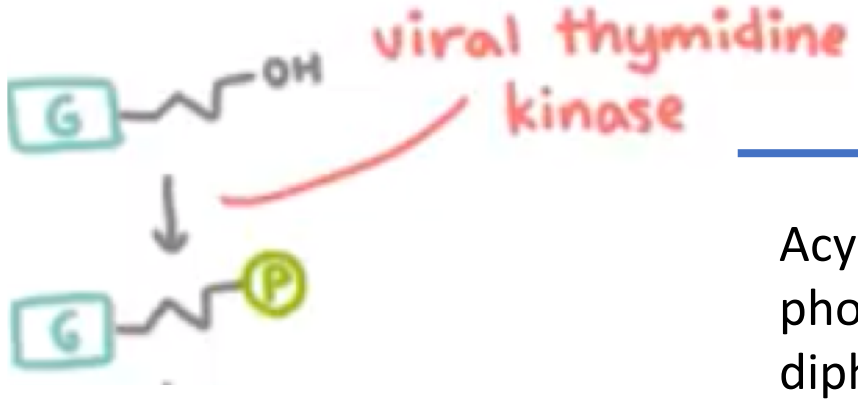
Treated into infected HSV



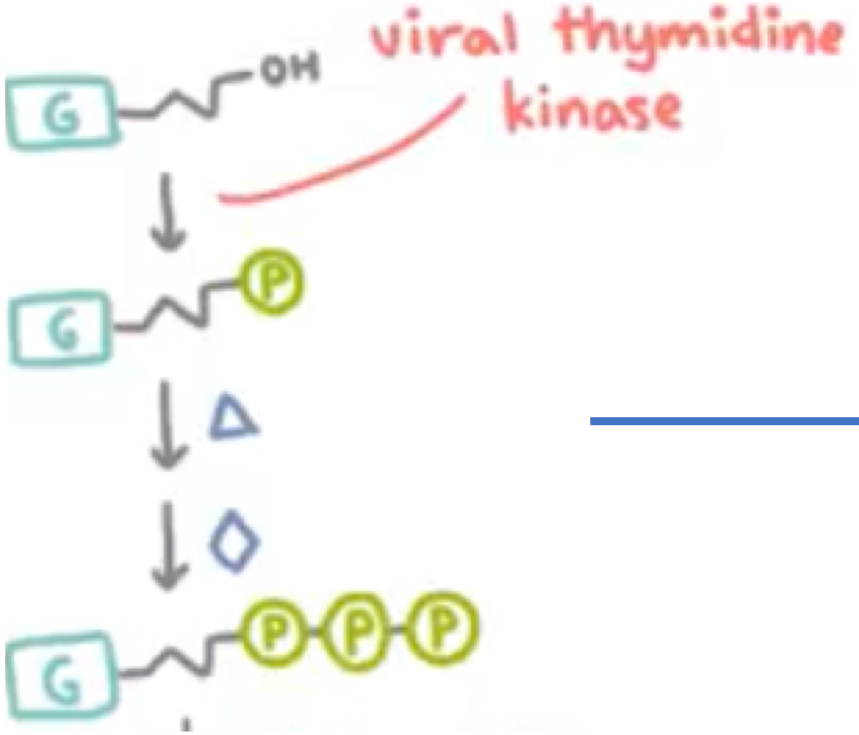
Acyclovir phosphorylated by viral thymidine kinase to **acyclovir monophosphate**

Human thymidine kinase does not recognize it

https://www.macrophage.co.

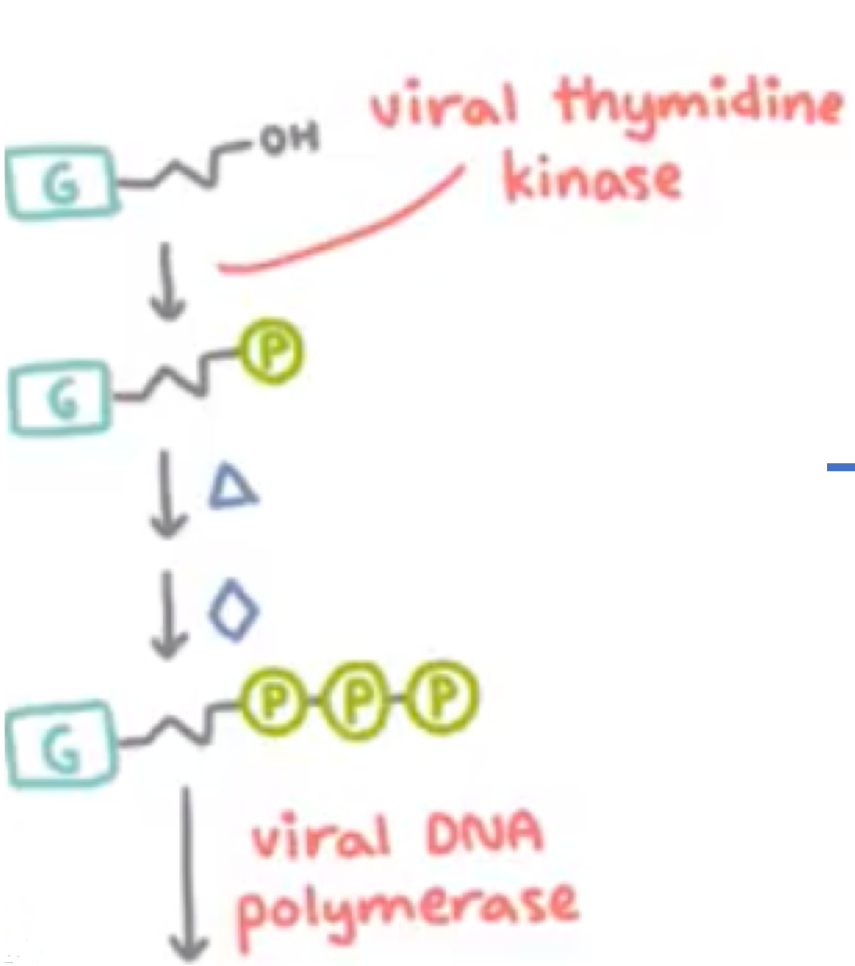


Acyclovir monophosphate phosphorylated into diphosphate and triphosphate

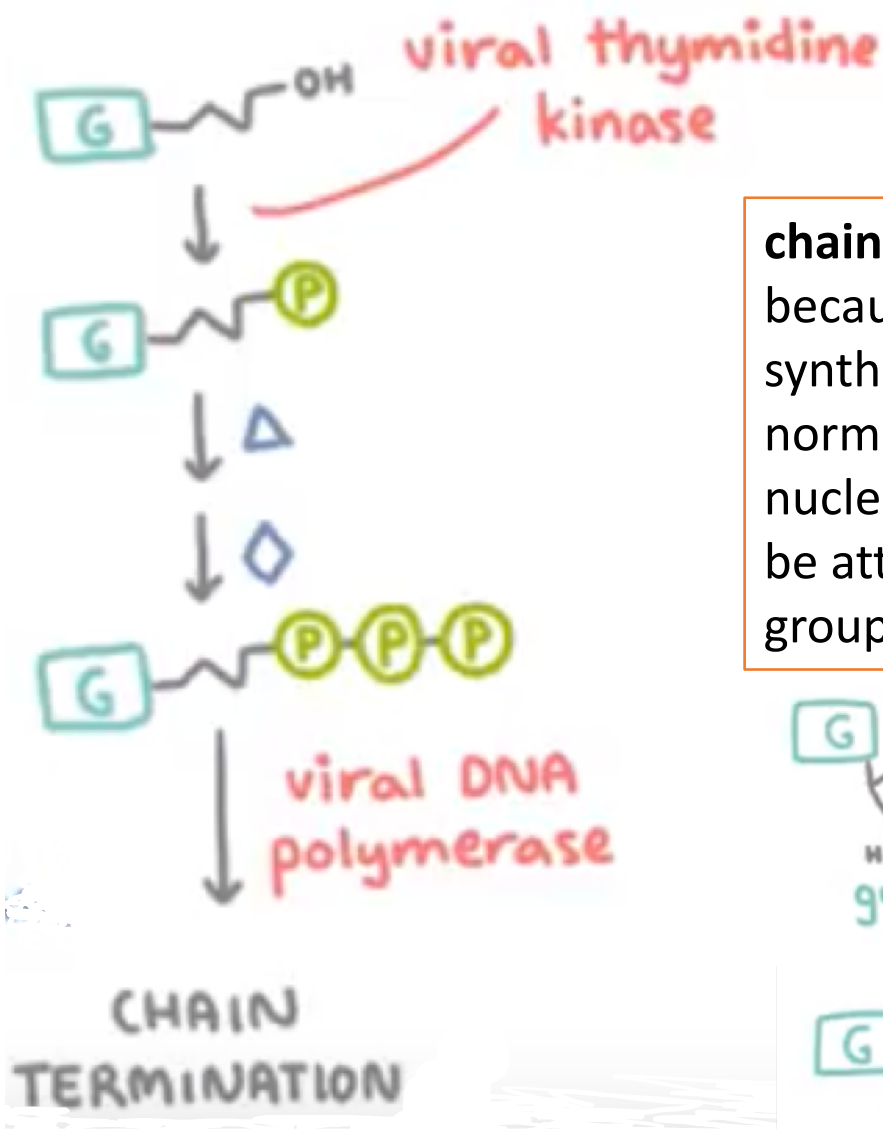


Become acyclovir triphosphate and the energy can be used by DNA polymerase to bind the acyclovir (guanosine analogue) to the DNA strand

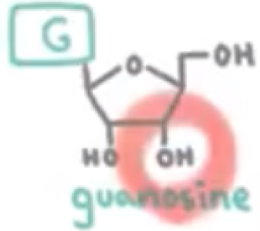
https://www.macrophage.co.

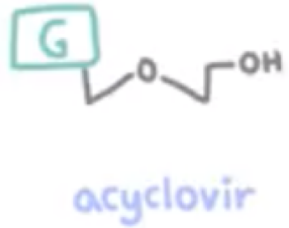


Cause **chain termination**



chain termination because in synthesizes DNA, normally the next nucleotide would be attach to 'OH' group in cyclic





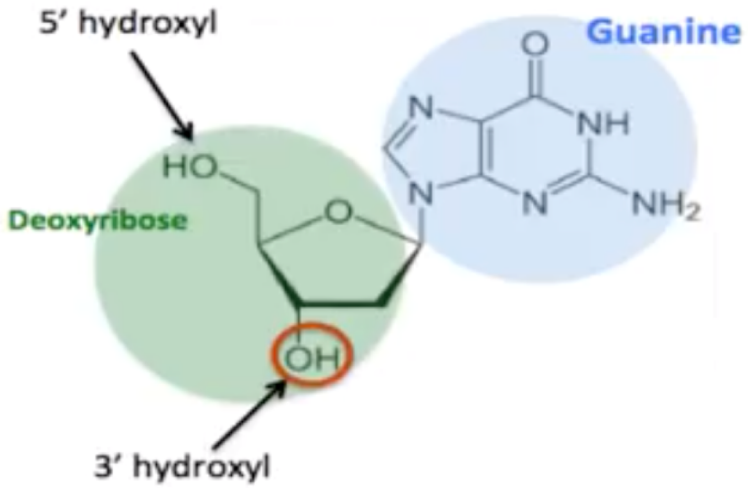
Binding the acyclovir (guanosine analogue) into strand DNA, **inhibit** the viral DNA polymerase

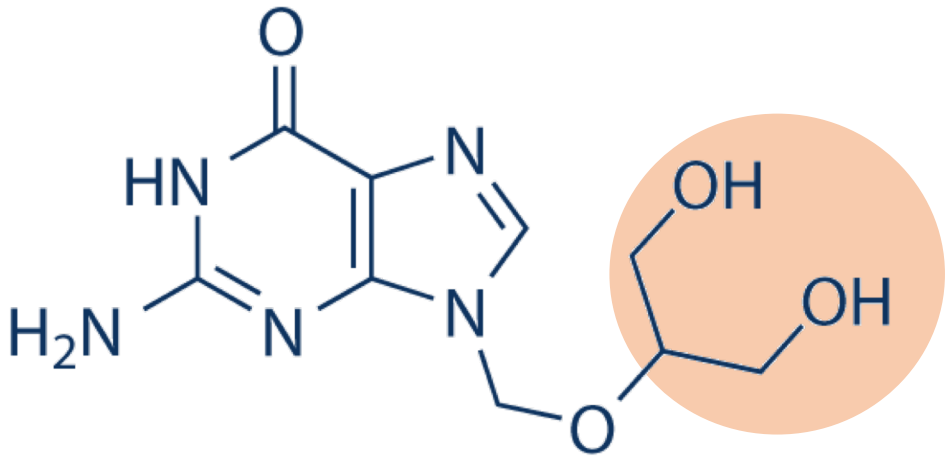
The viruses prevented from replicating

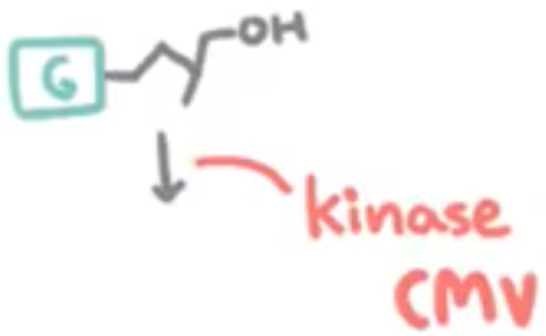
https://www.macrophage.co.

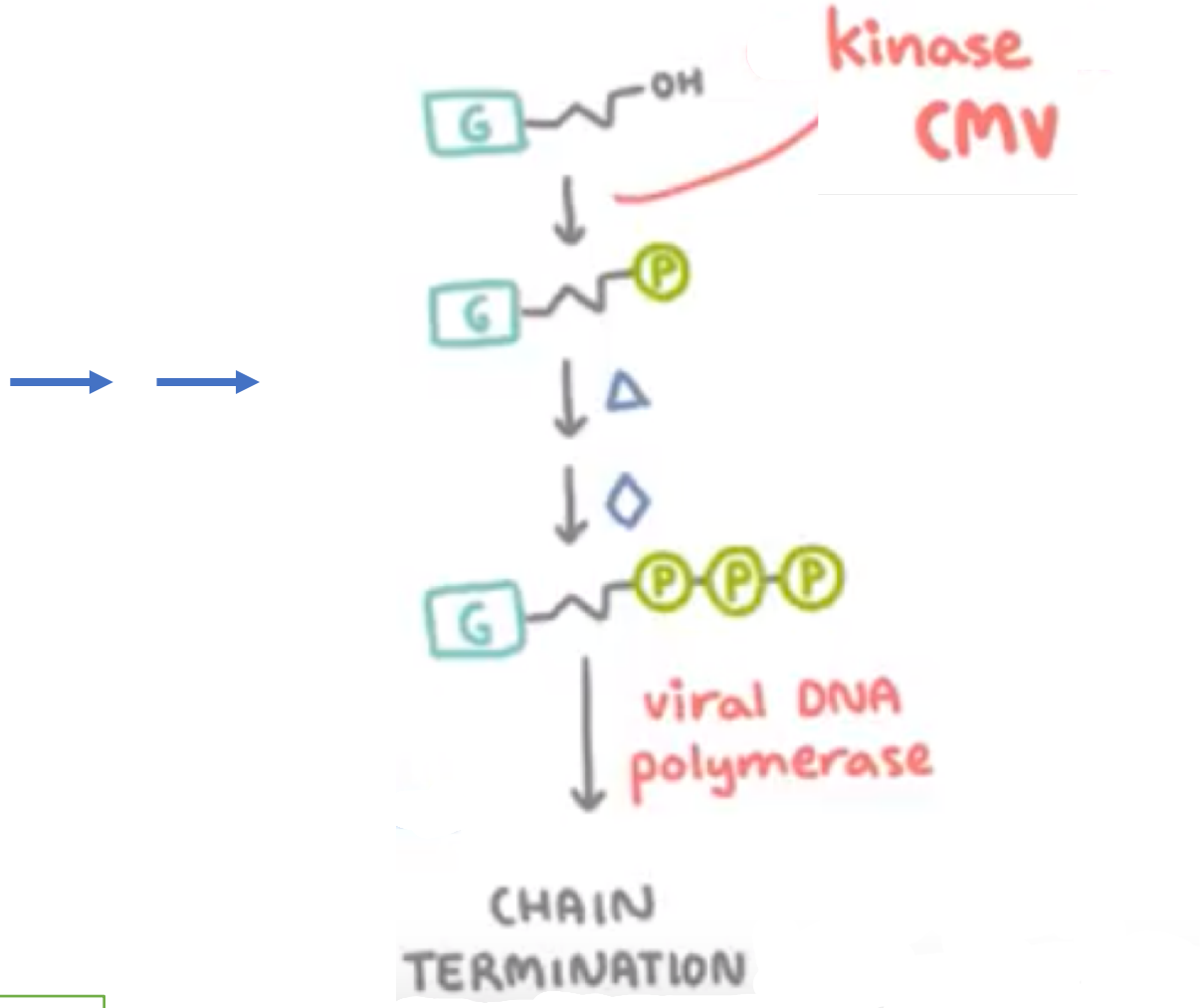
Ganciclovir

Ganciclovir is a guanosine analogue









In CMV, Ganciclovir has different kinase for phosphorylate : Kinase CMV

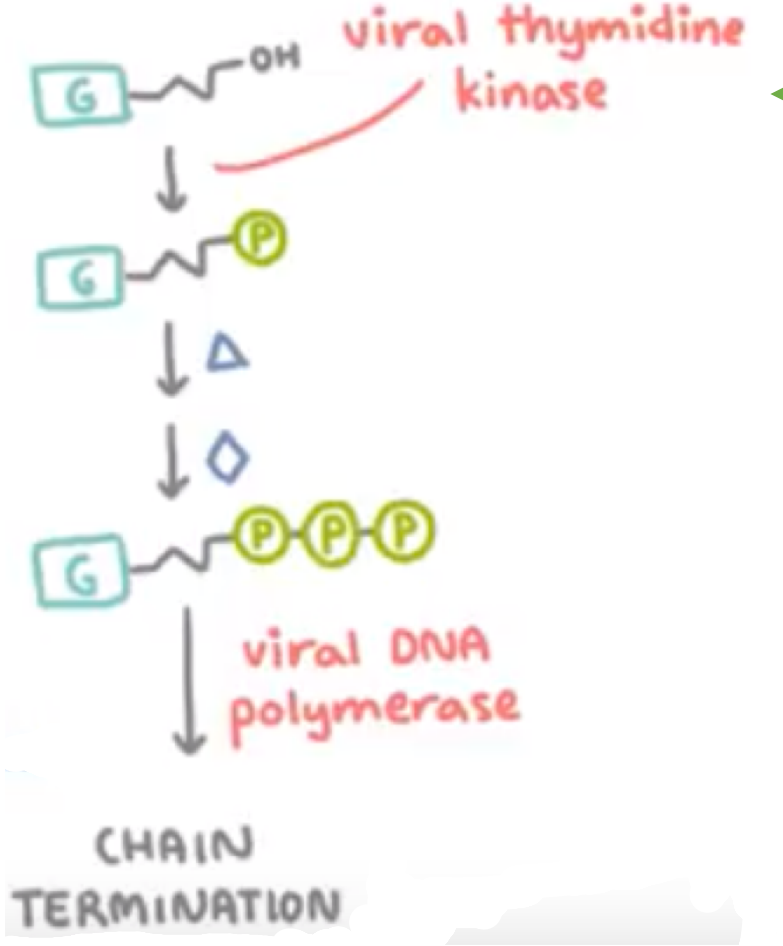
Generate ganciclovir triphosphate

In HSV and VZV, Ganciclovir could be phosphorylated by thymidine kinase, but not recommendation to use due to toxic

Specificity

- Uninfected cells do not phosphorylate acyclovir to acyclovir-5’-monophosphate
- Acyclovir triphosphate is more potent inhibitor of viral DNA polymerase than host cell enzyme
- The human DNA polymerase does not recognize the acyclovir triphosphate

Different between HSV, VZV, CMV



HSV VZV ~~CMV~~

Acyclovir does not work against CMV

Drugs	Pro-drugs	
acyclovir	valacyclovir	HSV/VZV » CMV
penciclovir	famciclovir	HSV/VZV
ganciclovir	valganciclovir	CMV > HSV/VZV

https://www.macrophage.co.

Antiherpesviral drug

1. Nucleoside analogs (acyclovir and ganciclovir) actually **mimic the normal nucleoside** and **block the viral DNA polymerase enzyme.**
2. Iidoxuridine are activated by **cellular enzymes human**, so these have less specificity.
3. Non-nucleoside inhibitors of herpesvirus replication include foscarnet, which **directly inhibits** the viral DNA polymerase and thus **blocks formation of new viral DNA**.
4. Docosanol (topical) **inhibit** herpes virus **attachment** to epithelial cells
5. Fomivirsen **inhibit** herpes virus **attachment** to epithelial cells and **inhibit virus replication** through an antisense mechanism → Binding of fomivirsen to the target mRNA, results in inhibition of protein synthesis, subsequently inhibiting virus replication.

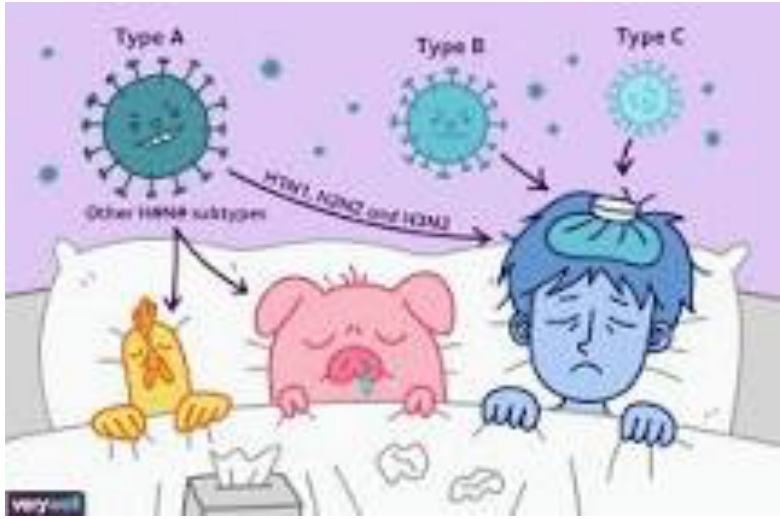
Anti-Influenza drug

Influenza

- Influenza is the (-)ssRNA-containing virus

Two type of Influenza :

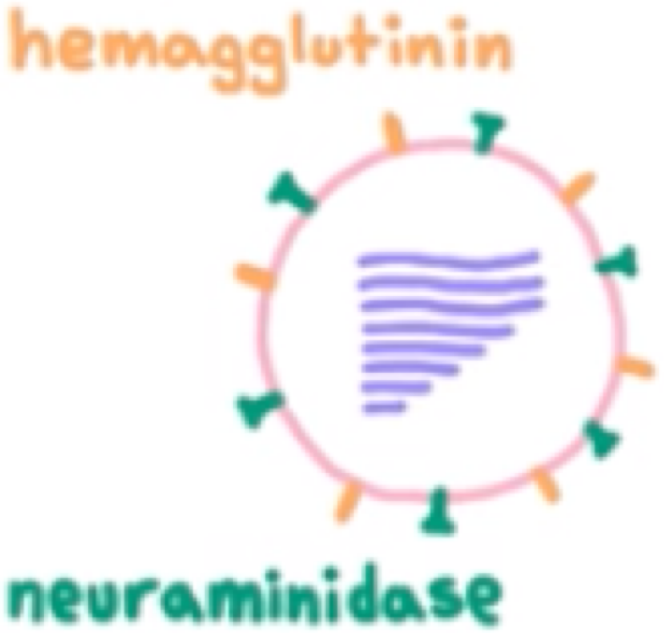
1. Influenza A : are capable of infecting animals
2. Influenza B : is found only in humans
3. Influenza C : milder than either type A or B



https://www.webmd.com/cold-and-flu/

Character of Influenza virus

1. (-) ssRNA
2. Segmented genome (there are eight strands of (-)RNA)
3. Enveloped with 2 kind protein hemagglutinin and neuraminidase



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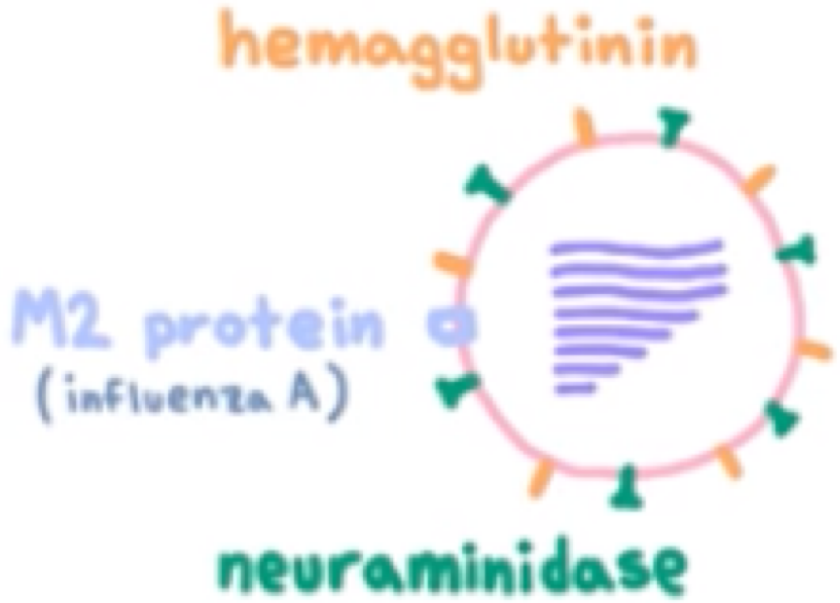
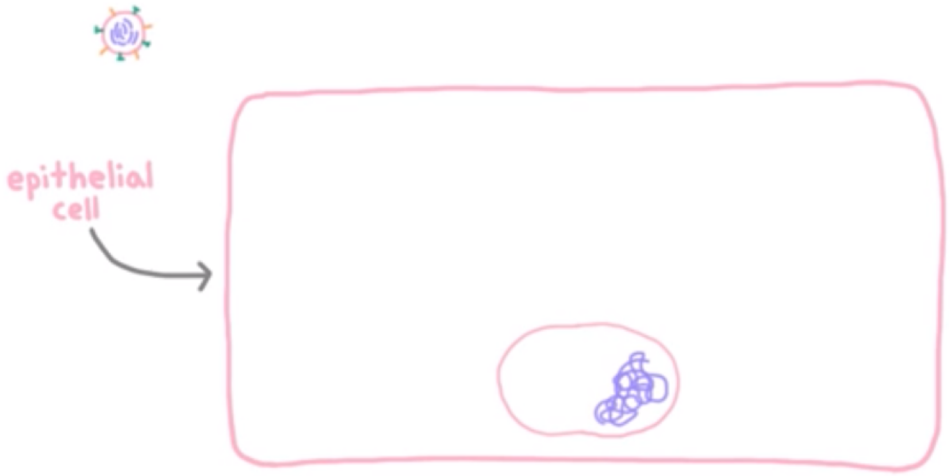
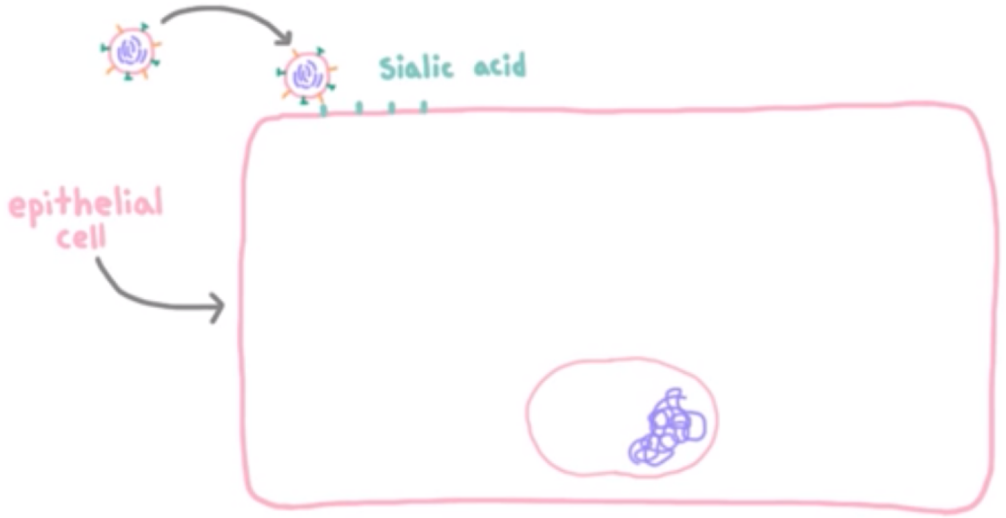


Influenza A

- Has an M2 ion channel that allow H+ ions to enter the virus itself and facilitate to fusion in endosome membrane into cytoplasm



Virus **attach**/infect the epithelial cells in the upper respiratory tract

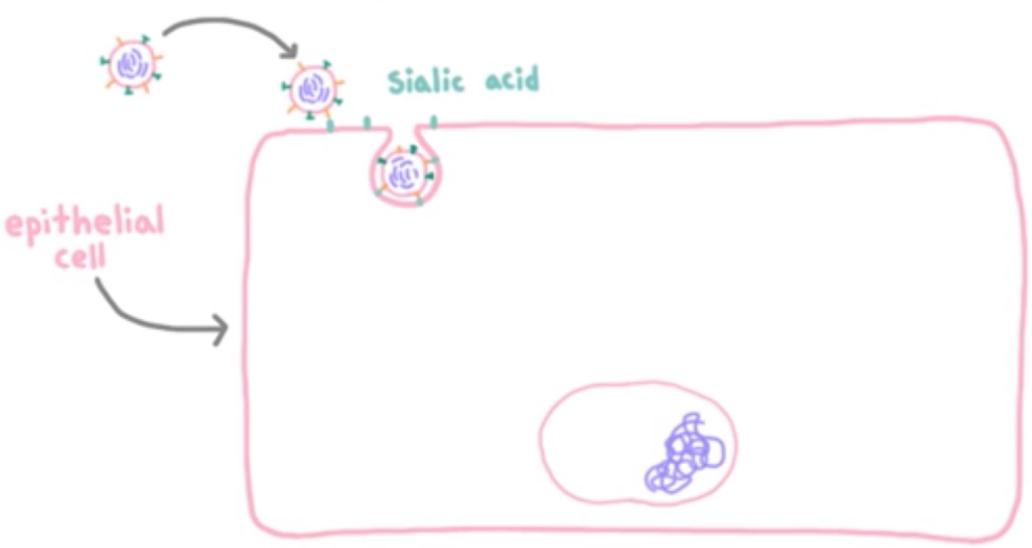


The attachment of virus through **binding of hemagglutinin of virus to sialic acid** in epithelial cells

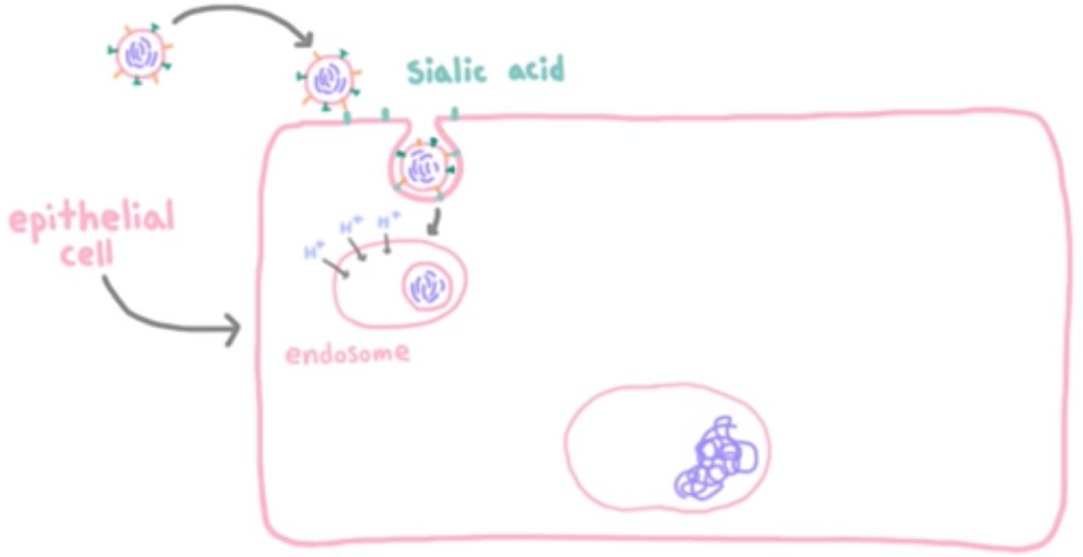
sialic acid : almost express in human cells function

Kosik, I. and Yewdell, J.W., 2019

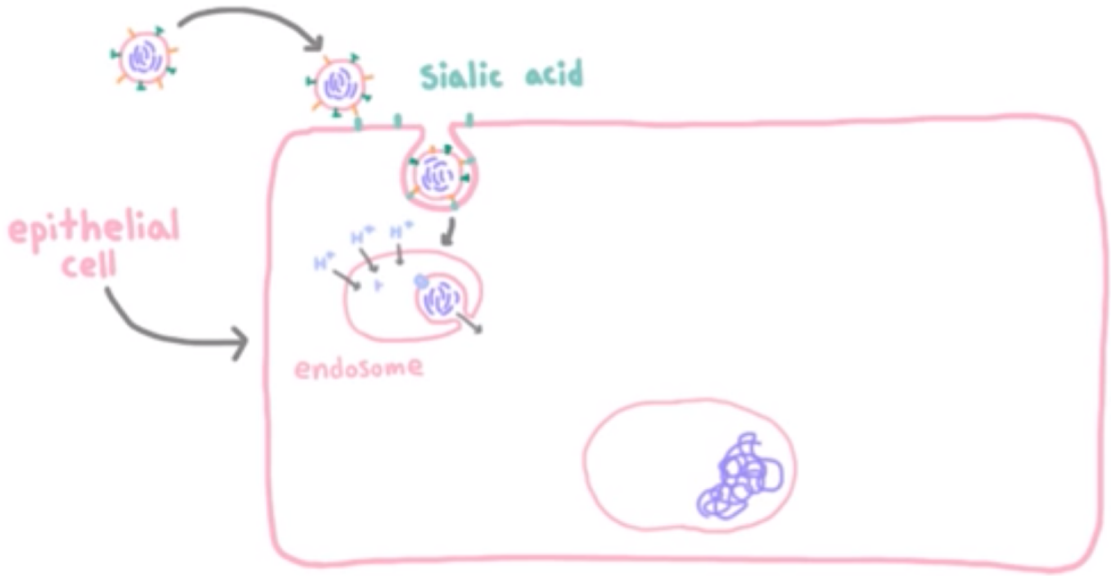
https://www.macrophage.co.

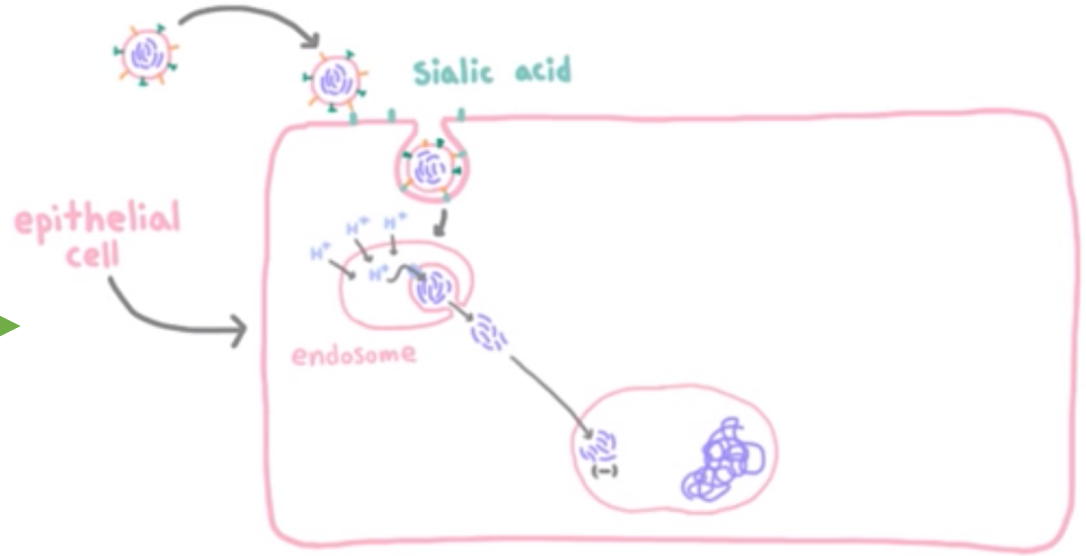


Virus taken up into the cells by receptor mediated endocytosis



Put the virus into endosome



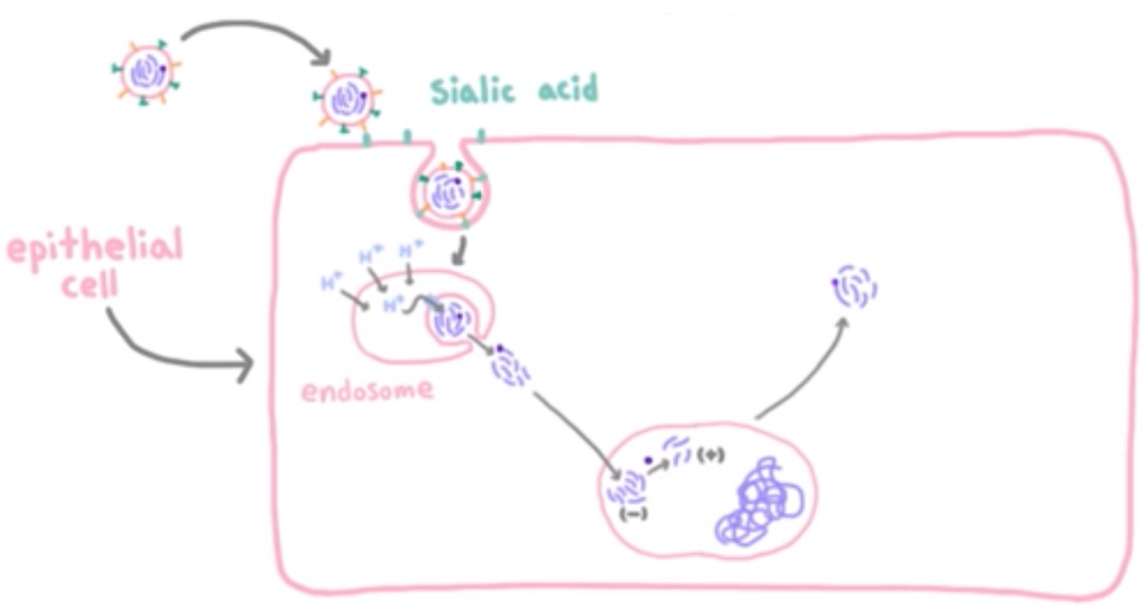


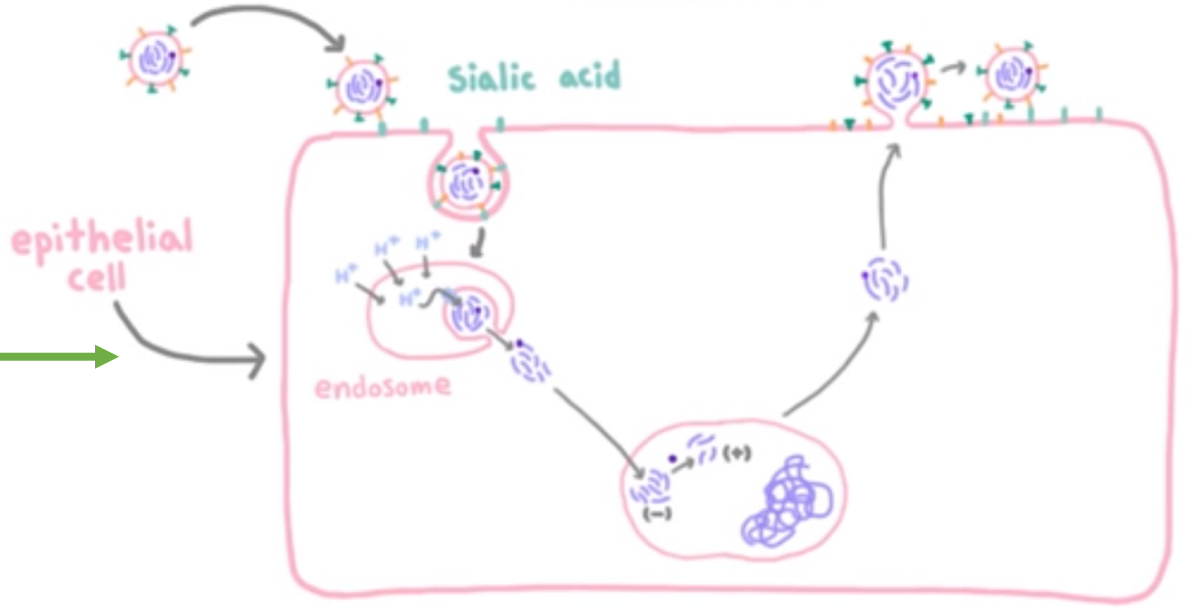
H+ ion enter into endosome
→ the envelope of virus fuse with endosome membrane

Viruses release its content into cytoplasm include genetic material which enter into nucleus

Viruses type is (-) strand should to convert (+) strand to create protein from virus itself

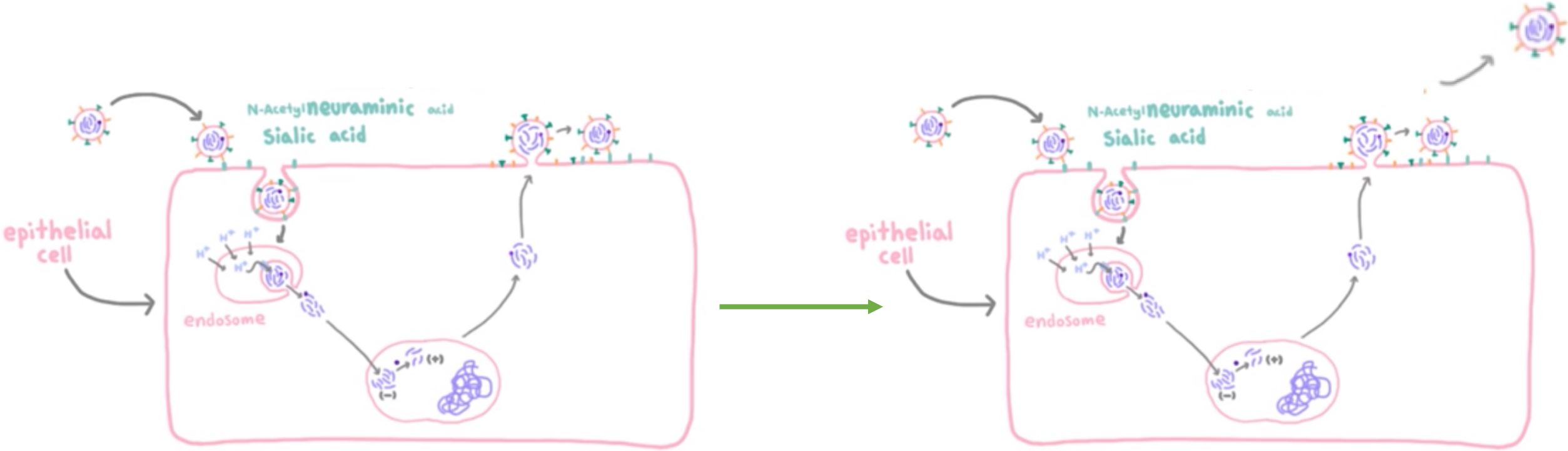
Viruses have RNA-dependent RNA polymerase in every particle





Viruses have RNA-dependent RNA polymerase in every particle. Then convert (-) RNA into (+) RNA → are translated into protein.
Replicate machinery of viruses.

Generated new variant from (-) RNA and release into cell membrane where hemagglutinin and neuraminidase were embedded



Sialic acid = N-acetylneuraminic acid, cut the binding of sialic acid with hemagglutinin off.

Viruses go free and infected new cells

Influenza agents medication

Inhibit neuraminidase and **prevent the release** of influenza virions from an infected host cells

decreases the release of virus from infected cells,
increases the formation of viral aggregates,
decreases the spread of the virus through the body.

If taken within 30 hours of the onset of influenza, both drugs can shorten the duration of the illness.

Occurrence of resistance is low.
Resistant occur due to specific histidine to tyrosine substitution in neuraminidase protein

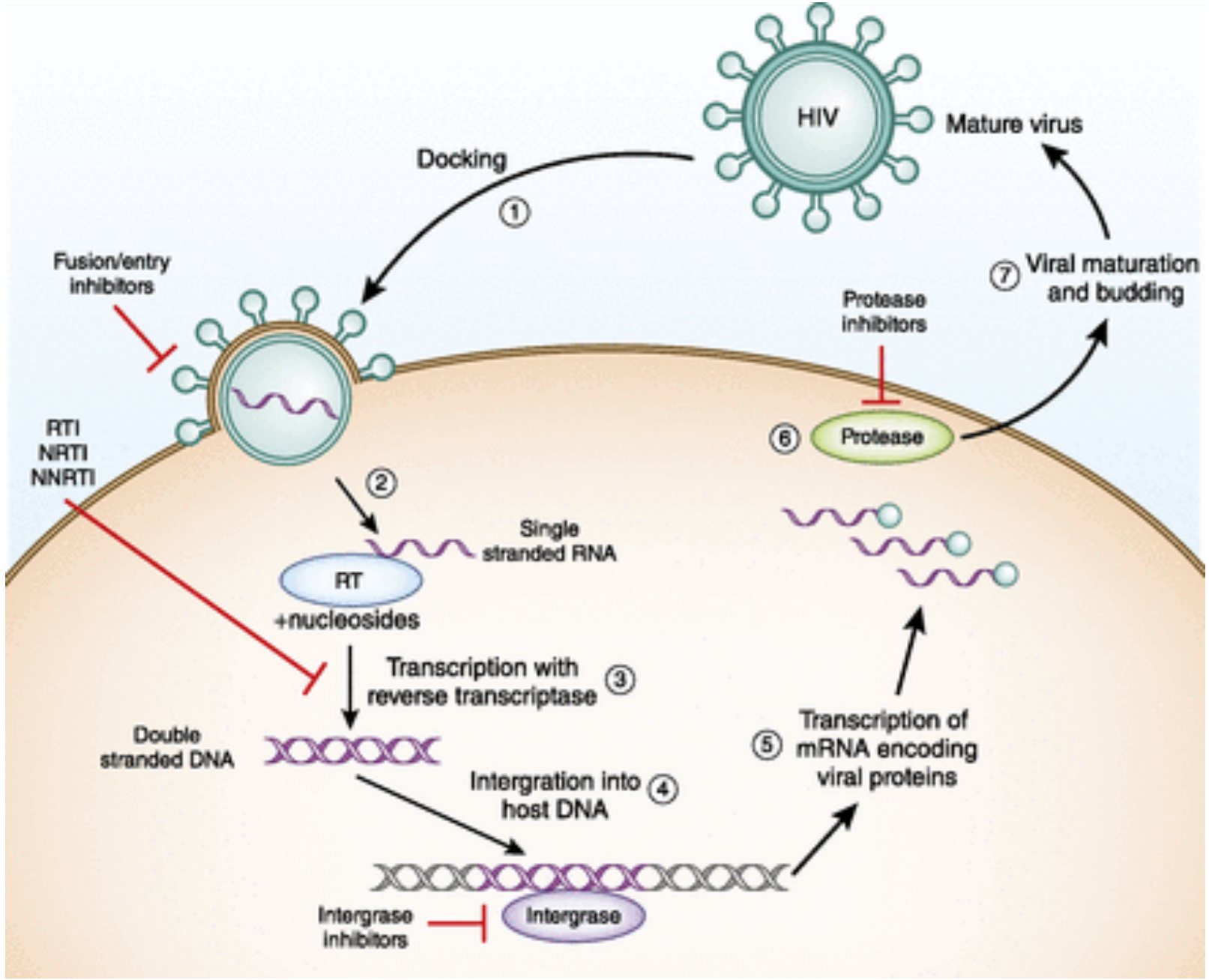
Influenza agents medication

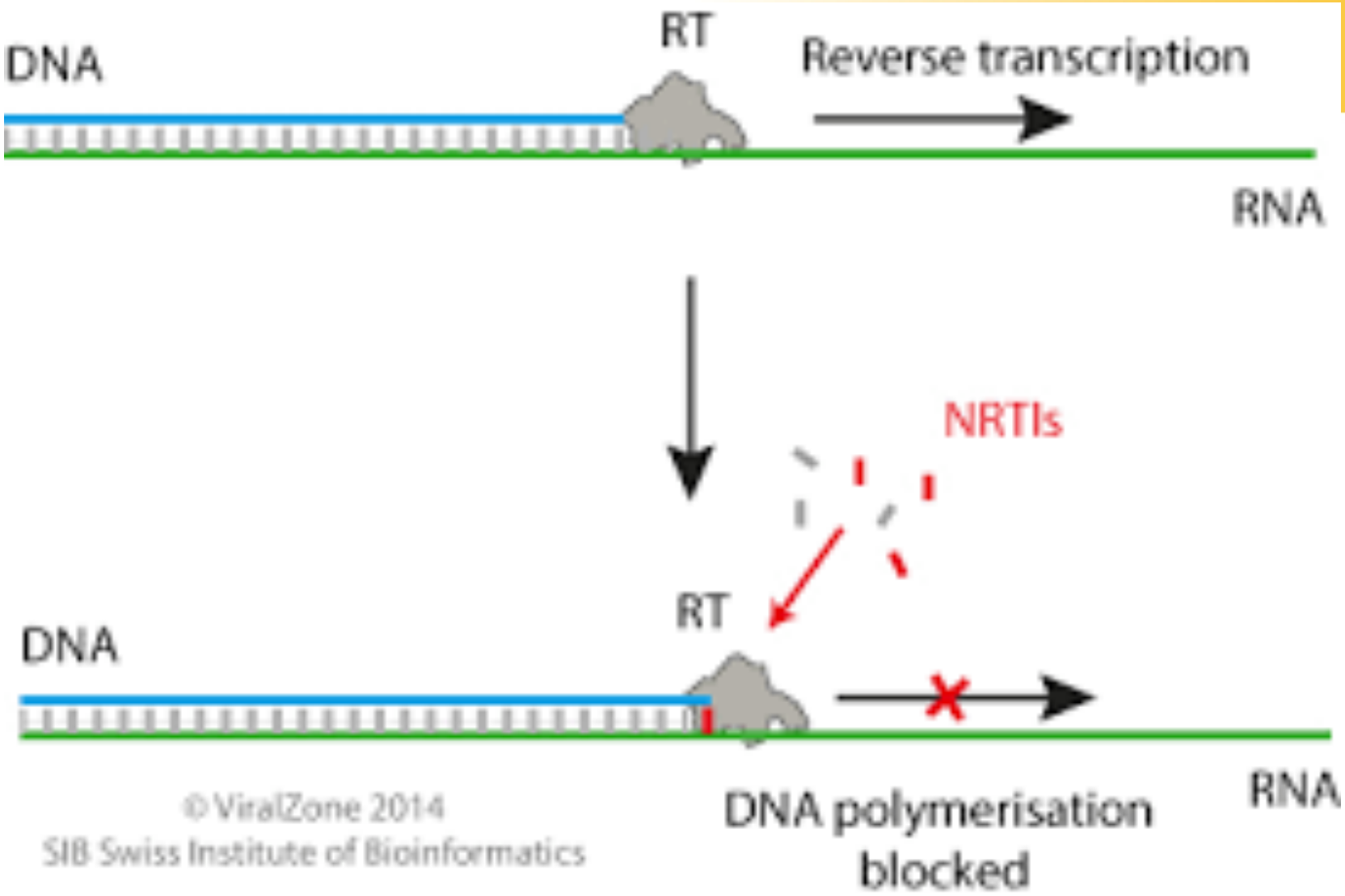
Amantadine and Rimantadine : **M2 channel blocker** specific in Influenza A

The action of amantadine is to **block** uncoating of the virus within the cell and thus **prevent the release** of viral RNA into the host cell.

Increasing the resistance in Influenza A strain

Anti-HIV


HIV
Mature virus
Docking
1
Fusion/entry inhibitors
RTI
NRTI
NNRTI
2
Single stranded RNA
RT
+nucleosides
Transcription with reverse transcriptase
3
Double stranded DNA
Intergration into host DNA
4
Intergrase
Intergrase inhibitors
5
Transcription of mRNA encoding viral proteins
6
Protease
Protease inhibitors
7
Viral maturation and budding



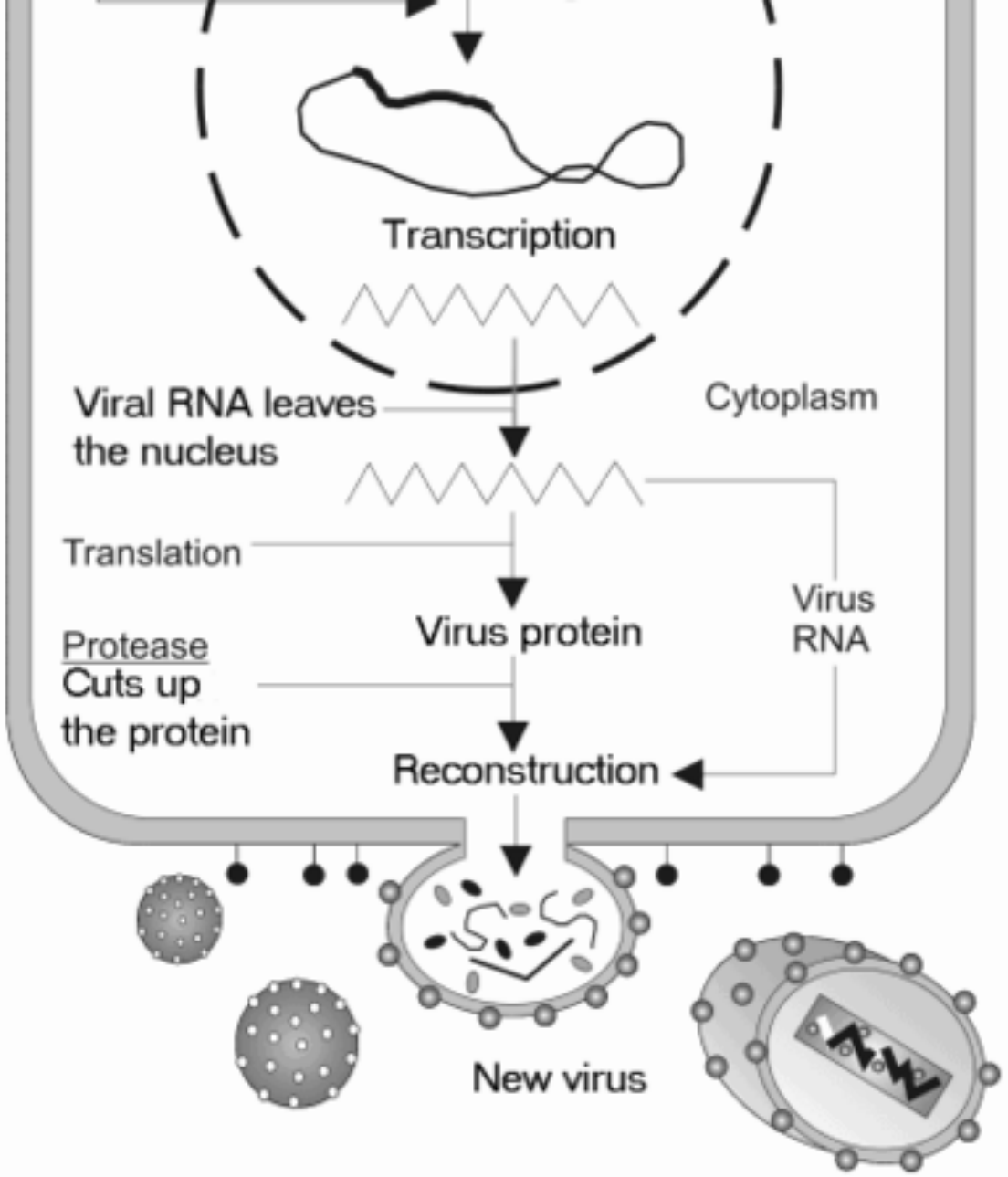
RTIs come in three forms:

- Nucleoside analog reverse-transcriptase inhibitors (NARTIs or NRTIs)
- Nucleotide analog reverse-transcriptase inhibitors (NtARTIs or NtRTIs)
- Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)
- Nucleoside reverse transcriptase translocation inhibitor (NRTTIs)

Resume

- Human immunodeficiency virus (HIV), the virus that causes AIDS, is a retrovirus.
- HIV contains reverse transcriptase, an enzyme that converts viral RNA into DNA that integrated into the DNA of the host cell.
- Reverse transcriptase(RT) inhibitors work by blocking the action of reverse transcriptase.
- There are two groups of RT inhibitors.

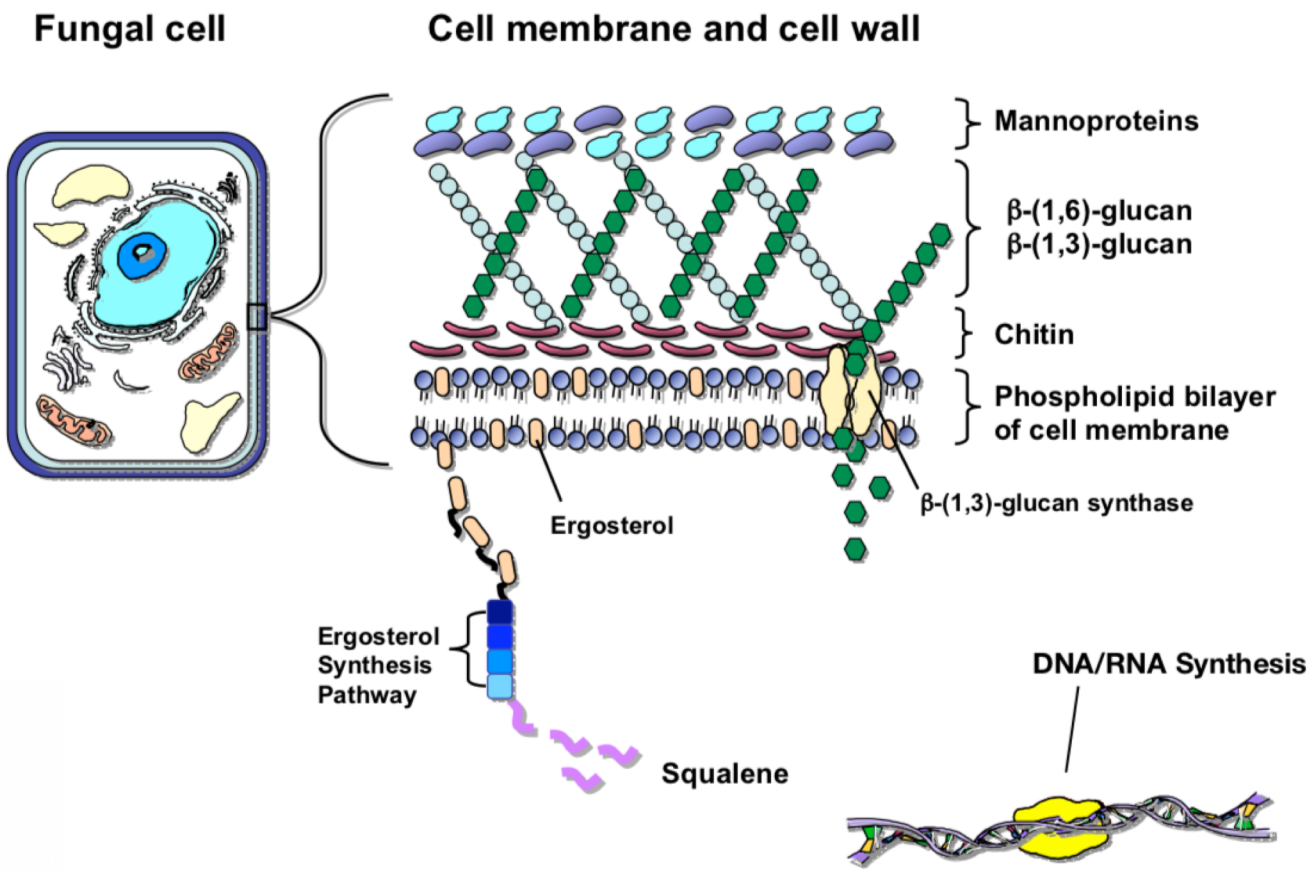
1. Nucleoside RT inhibitors (e.g., zidovudine, didanosine, zalcitabine, lamivudine, and stavudine) → **be phosphorylated (**active). These drugs mimic the normal nucleosides and block reverse transcriptase. Because the different nucleoside RT inhibitors mimic different purines and pyrimidines, use of two of the drugs in this group is more effective than one alone.
2. The second group of RT inhibitors are the non-nucleoside inhibitors (e.g., delaviridine, efanvirenz, and nevirapine), which do not require activation and, because they act through a different mechanism, exhibit a synergistic inhibition of HIV replication when used with the nucleoside RT inhibitors.



Protease inhibitors (e.g., ritonavir, saquinavir, and indinavir) block the spread of HIV to uninfected cells by inhibiting the viral enzymes involved in the synthesis of new viral particles.

Anti-fungal

Fungal and Anti-fungal

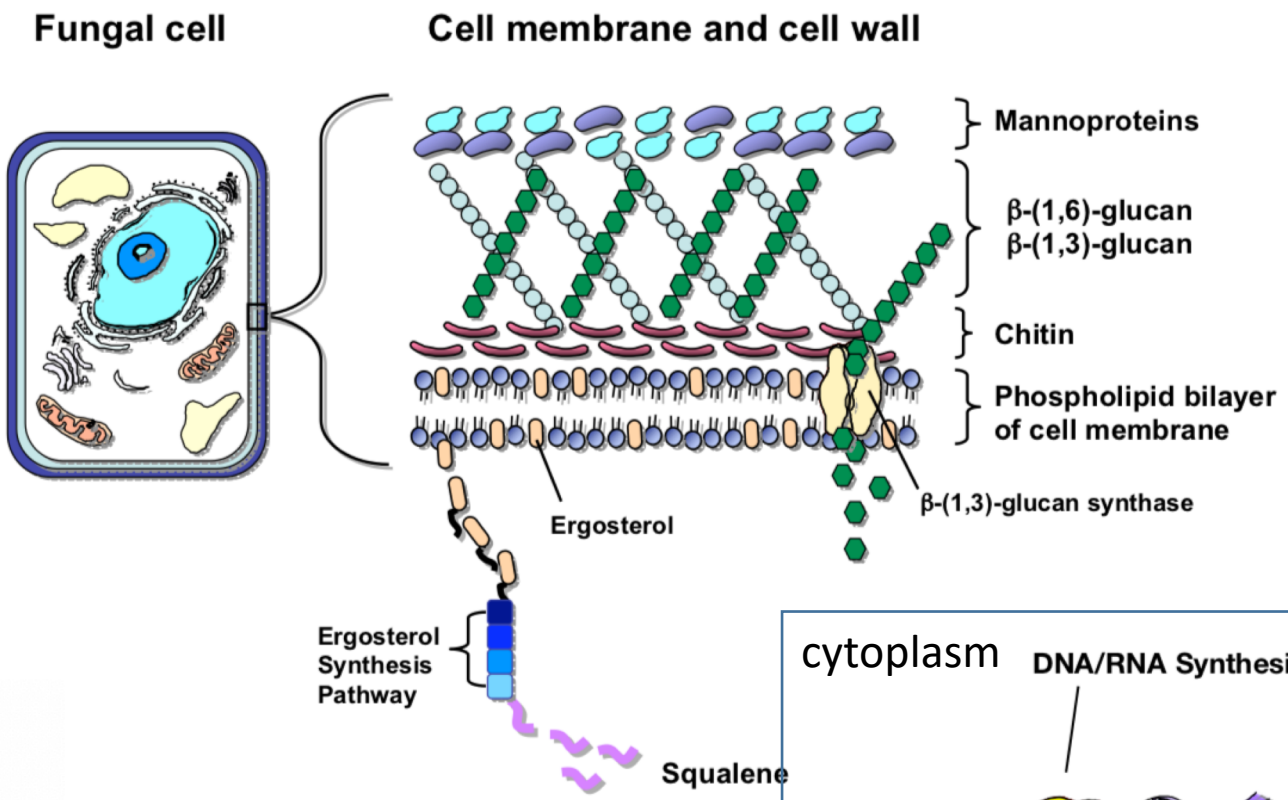


Cell wall :

- Chitin
- Protein
- B-glucan

Synthesis of ergosterol begins with conversion of squalence into squalene epoxide by squalene epoxidase → converted into Levonosterol → converted into ergosterol by 14-a sterol gemethylase

Fungal and Anti-fungal



cytoplasm DNA/RNA Synthesis → RNA synthase – RNA for protein synthiseze

Centriol : division mitosis to produce microtubule

ANTIFUNGAL DRUGS
classes

- **POLYENES**
  Amphotericin B, nystatin
- **AZOLES**
  Imidazoles: Ketoconazole..
  Triazoles: Fluconazole,
  itraconazole,
  voriconazole,
  posaconazole,
  ravuconazole
- **ALLYLAMINES**
  Terbinafine, butenafine
- **MORPHOLINE**
  Amorolfine
- **FLUORINATED PYRIMIDINE**
  Flucytosine
- **ECHINOCANDINS**
  Caspofungin,
  anidulafungin,
  micafungin
- **PEPTIDE-NUCLEOSIDE**
  Nikkomycin Z
- **TETRAHYDROFURAN DERIVATIVES**
  Sordarins, azasordarins
- **OTHER**
  Griseofulvin

Antifungal drug

1. Inhibit squalene epoxidase : Terbinafine
2. Inhibit 14-a sterol gemethylase : Azoles
3. Inhibit of B glucan synthase : Echinocandins
4. Inhibitor RNA synthase : Tavaborone
5. Inhibitor of microtubule : Griseofulvin

Amphotericin B

• Mechanism: binds sterols, preferentially ergosterol, and disrupts osmotic integrity of cell membrane

Azoles

• Mechanism: block ergosterol synthesis via inhibition of cytochrome P450 dependent 14α-demethylase (Erg11)

Golongan Imidazole dan triazole

Ketoconazole, fluconazol, Butoconazole, Econazole, Miconazole, Oxiconazole, sertaconazole, sulconazole (bekerja dengan menghambat 14a-sterol demetilase yang mengubah lanosterol menjadi ergosterol)

Allylamines, morpholines

• Mechanism: block ergosterol synthesis via inhibition of squalene epoxidase (allylamines), sterol reductase and isomerase activity (morpholines)

Golongan allylamine dan benzylamine

terbinafine, naftifine, butenafine (menghambat squalen epoksidase)

Echinocandins

• Mechanism: block cell wall synthesis via β-1,3 glucan synthesis inhibition

Antimetabolites

• Mechanism: block fungal DNA and protein synthesis (Flucytosine), fungal mitosis (Griseofulvin)