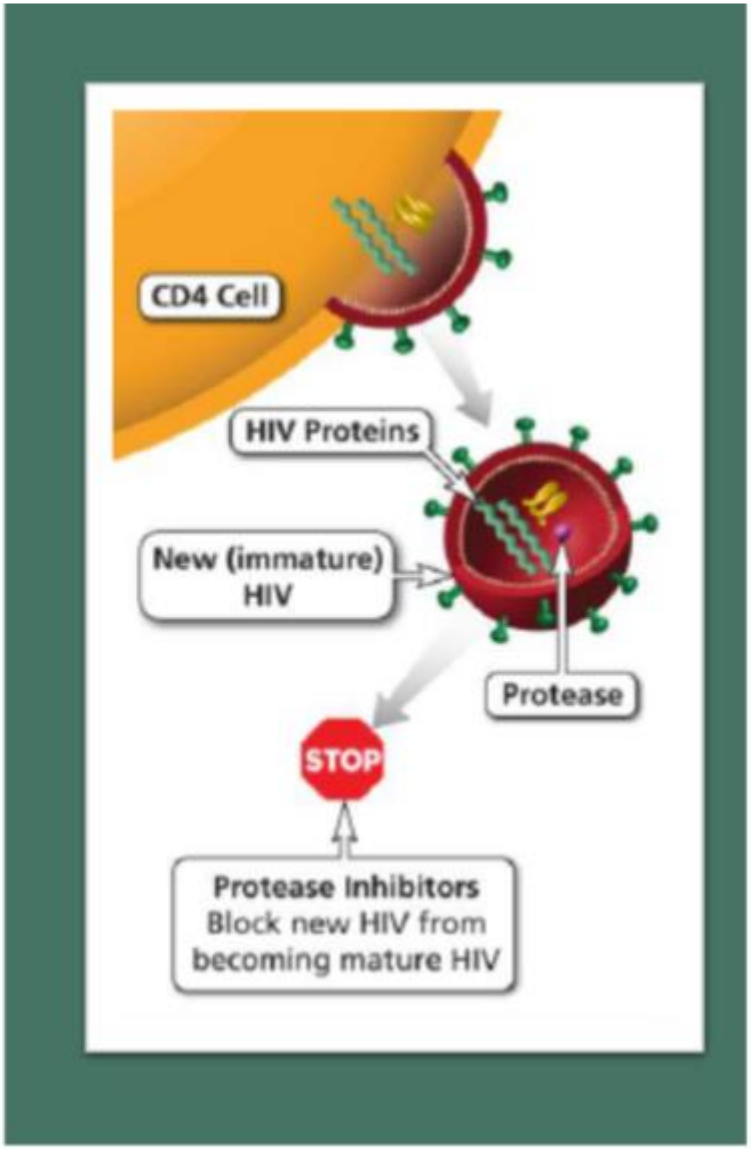
5. Protease inhibitors:

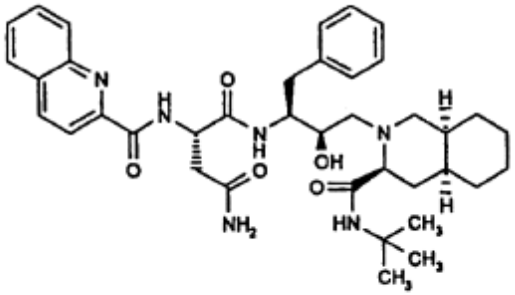
-the use of X-ray crystallography and molecular modelling led to the structure-based design of a series of inhibitors which act on the viral enzyme HIV protease.

-They have a short-term benefit when they are used alone, but resistance soon develops.

-When protease and reverse transcriptase inhibitors are used together, the antiviral activity is enhanced and viral resistance is slower to develop.

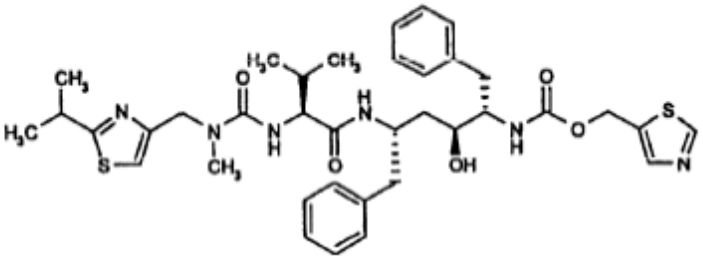


Commercial PI Drugs



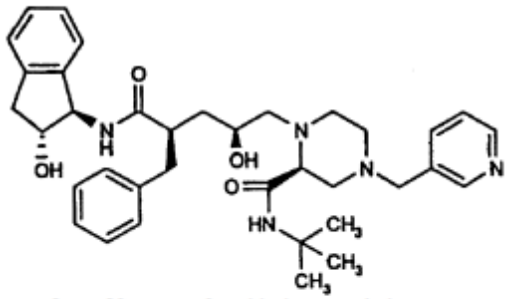
Saquinavir (Roche)

- first PI on the market
- rapid development of resistance
- low oral bioavailability
- strong binding to plasma proteins



Ritonavir (Abbott)

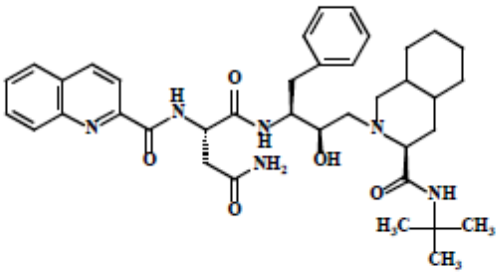
- although larger than Saquinavir displays better bio-availability
- potent inhibitor of cytochrom CYP3A4 and hence shuts down its own metabolism
- good in combination with other PIs
- strong binding to plasma proteins



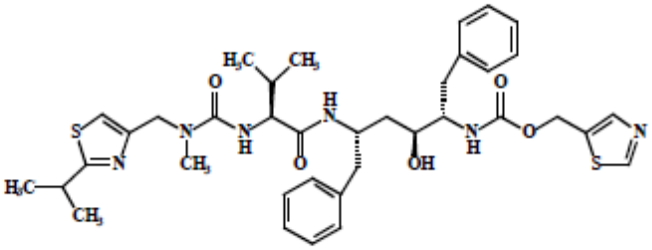
Indinavir (Merck)

- was designed based on Saquinavir
- better oral bioavailability
- less binding to plasma proteins

HIV protease Inhibitors

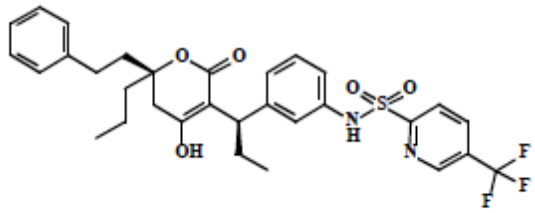


Saquinavir
hard gel capsules, Invirase ®
soft gelatin capsules, Fortovase ®



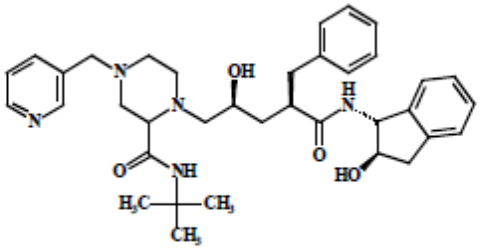
Ritonavir

Norvir ®



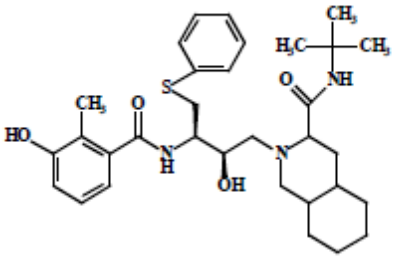
Tipranavir (U-140690)

Aptivus ®



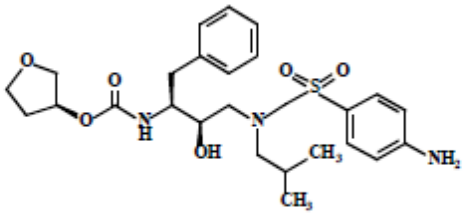
Indinavir

Crixivan ®



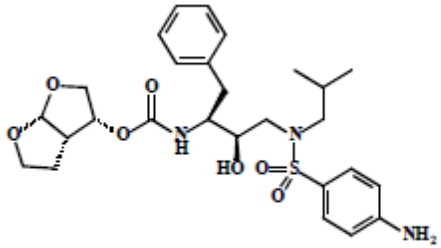
Nelfinavir

Viracept ®

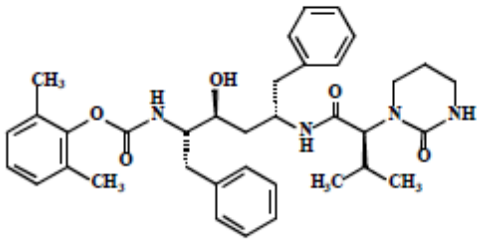


Amprenavir

Agenerase ® Prozei ®



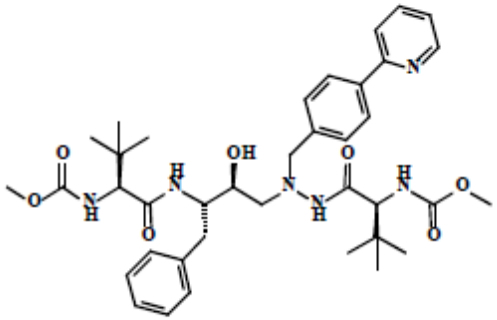
Darunavir (TMC-114)
Prezista ®



Lopinavir

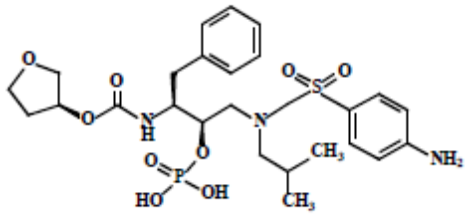
combined with ritonavir at 4/1 ratio

Kaletra ®



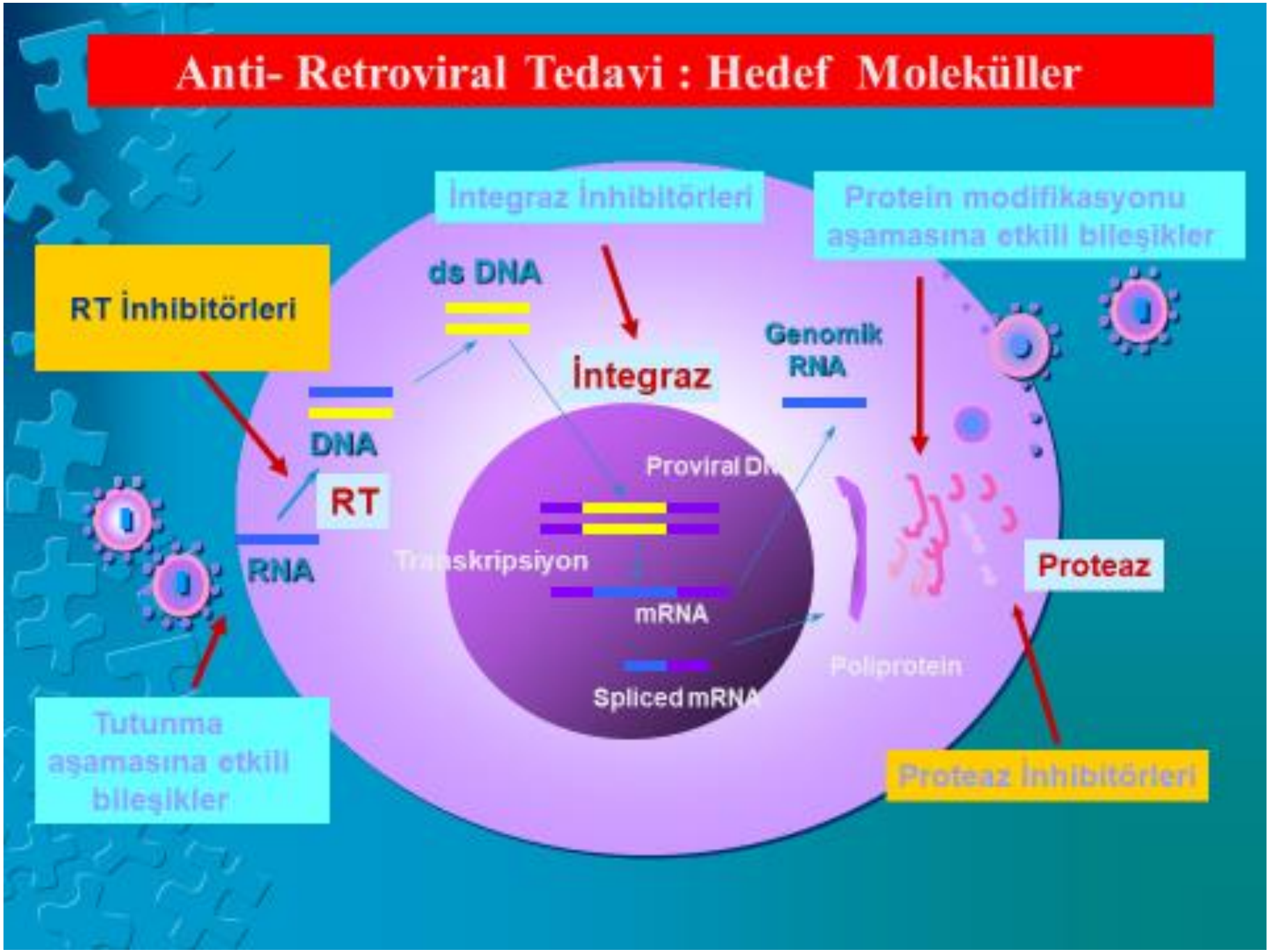
Atazanavir

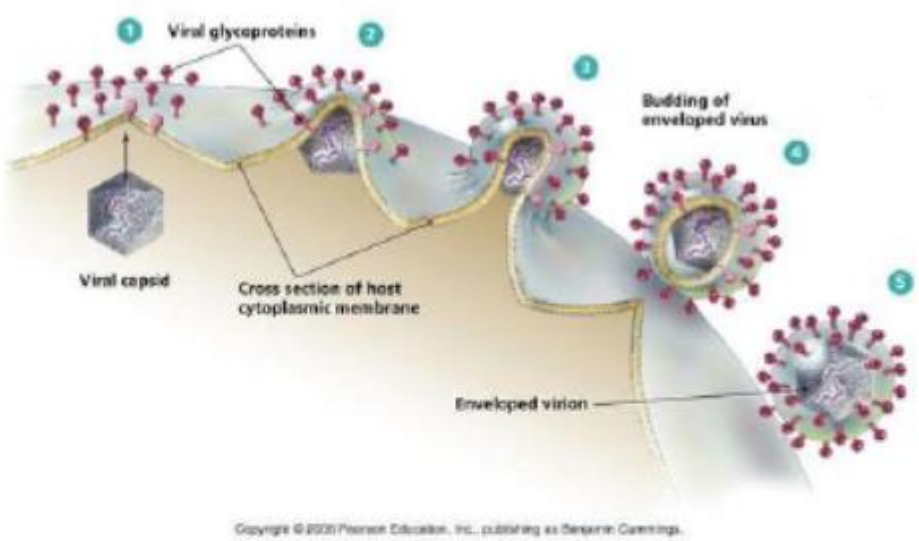
Reyataz ®



Fosamprenavir

Lexiva ® Telzir ®


Anti- Retroviral Tedavi : Hedef Moleküller
İntegraz İnhibitörleri
Protein modifikasyonu aşamasına etkili bileşikler
RT İnhibitörleri
ds DNA
Genomik RNA
İntegraz
DNA
RT
Proviral DN
RNA
Transkripsiyon
Proteaz
mRNA
Poliprotein
Spliced mRNA
Tutunma aşamasına etkili bileşikler
Proteaz İnhibitörleri

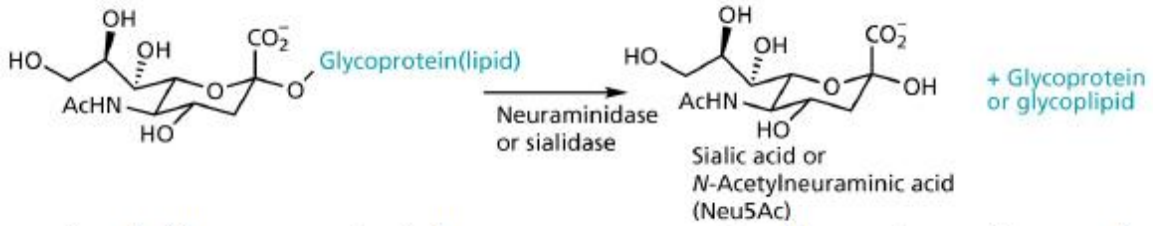


- Drugs use to prevents the Neuraminidase proteins on the surface of IV removing sialic acid from sialic aid-contanining receptors .
- Viral budding and downstream replication of IV are inhibited when sialic acid remains on the virion membrane and host cell.
- This segment will focus on the synthesis of the anti-influenza compound.
- available drugs : Zanamivir and oseltamivir.

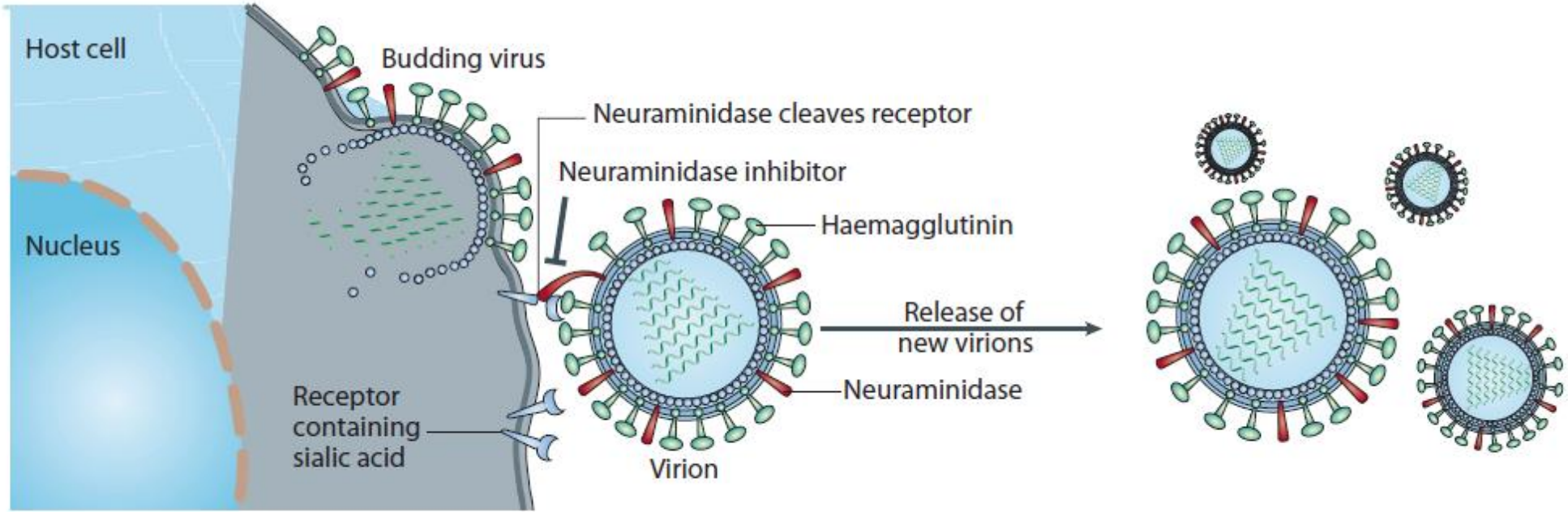
6. Release Inhibitors

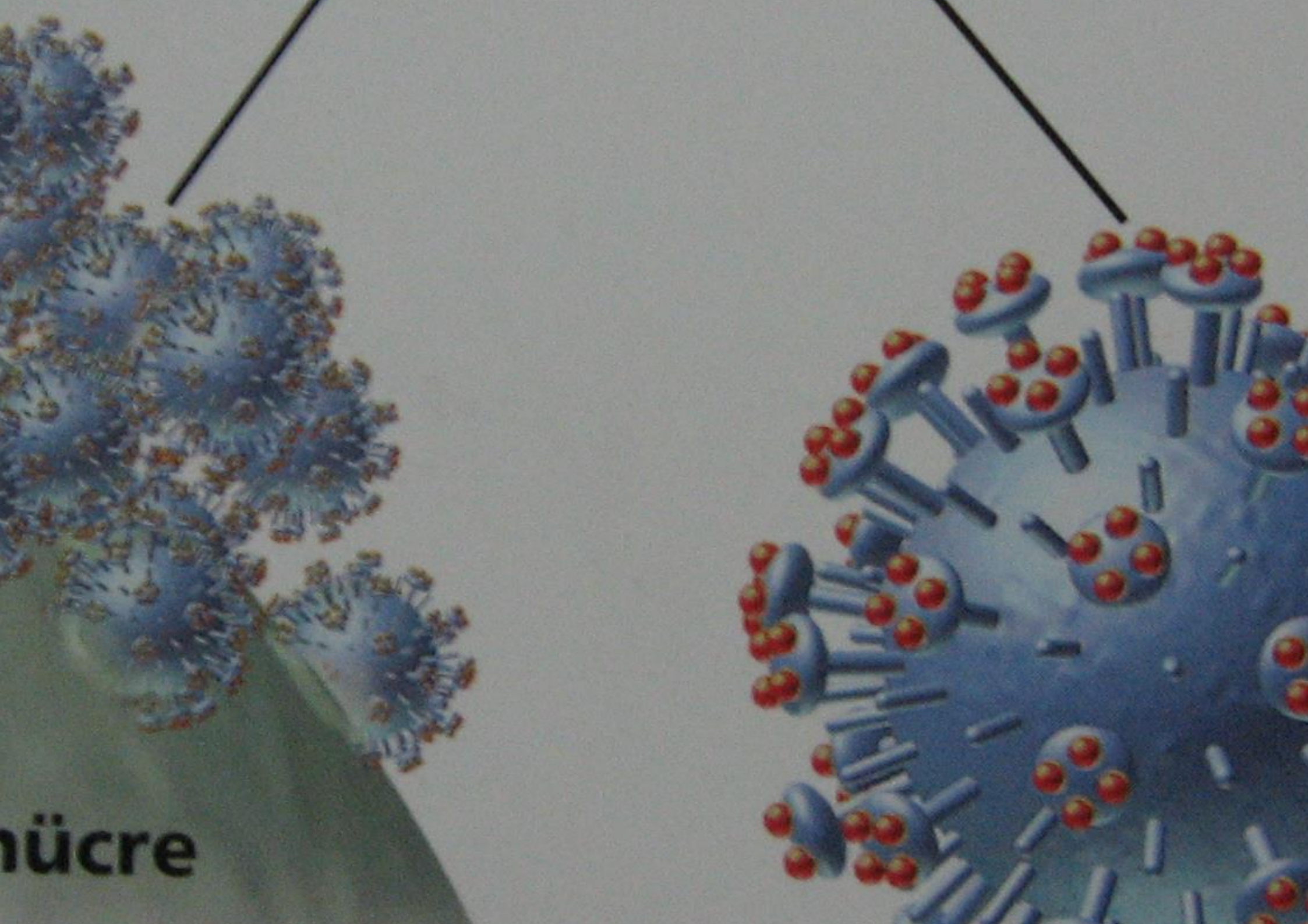
Viral Neuraminidase Inhibitors (Flu)

- The influenza virus binds to the target cell via interaction of its surface glycoprotein, haemagglutinin, with the host-cell surface receptor, that contains sialic acid. Another viral glycoprotein, neuraminidase, cleaves off the terminal sialic acid, allowing the virus to leave the cell once the virus has replicated:

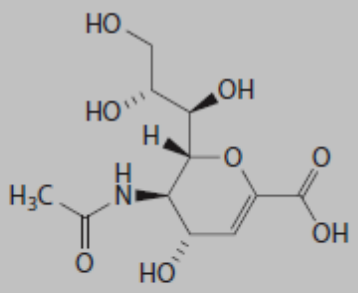


- Inhibiting the viral Neuraminidase prevents the virus from leaving the cell and infecting others.

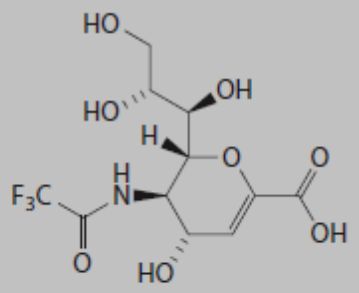



nücre

Commercial Neuraminidase Inhibitors



DANA



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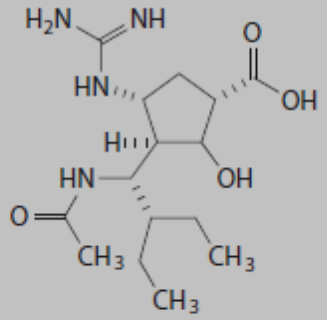
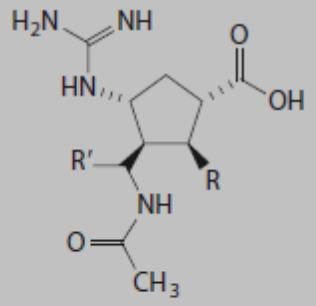
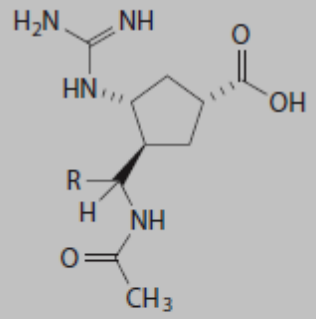


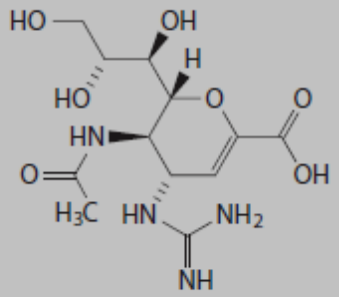
Peramivir
RWJ-270201



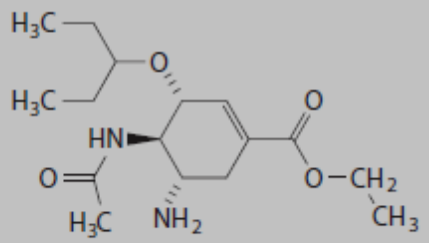
Cyclopentane
derivative



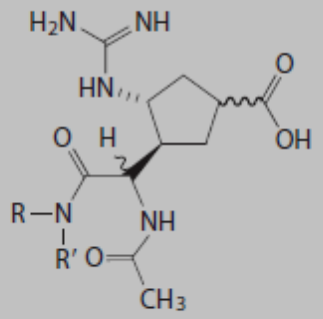
Cyclopentane
derivative



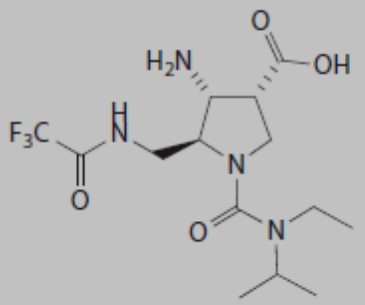
Zanamvir
(Relenza)



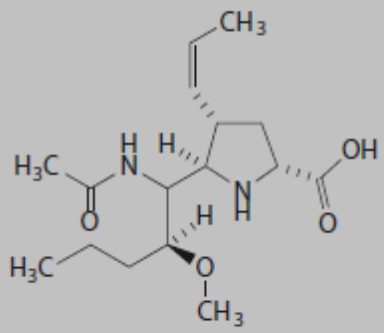
Oseltamivir
(Tamiflu)



Cyclopentane amide
derivative



Pyrrolidine derivative
A-192558

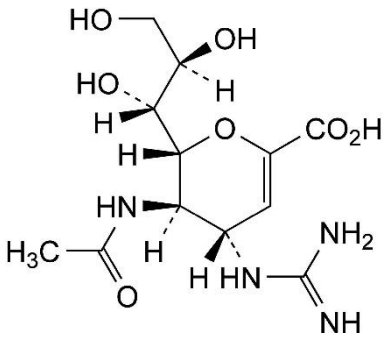


A-315675

Zanamivir

- Effective for both influenza A and B.
- Poor bioavailability and poor plasma portion binding
- Use oral inhalation

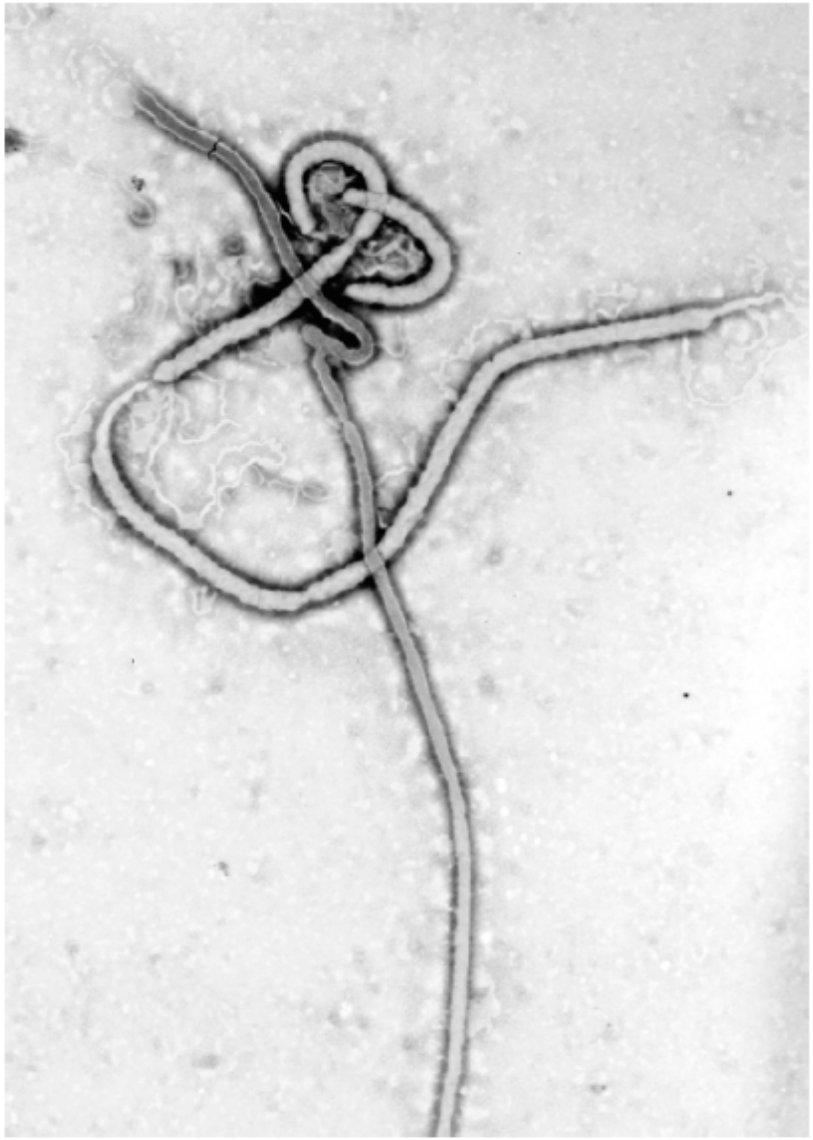
4-guanidino-2,4-dideoxy-2,3-dehydro-Nacetyl neuraminic acid



, $x\ H_2O$

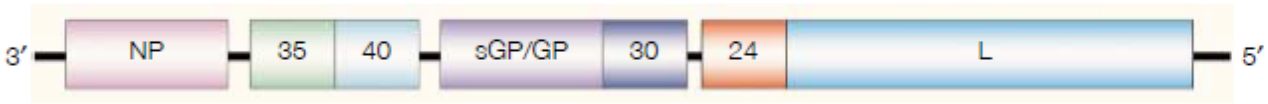
(2R,3R,4S)-3-(Acetylamino)-4-carbamimidoylamino-2-[(1R,2R)-1,2,3-trihydroxypropyl]-3,4-dihydro-2H-pyran-6-carboxylic acid.

The recent Ebola Outbreak

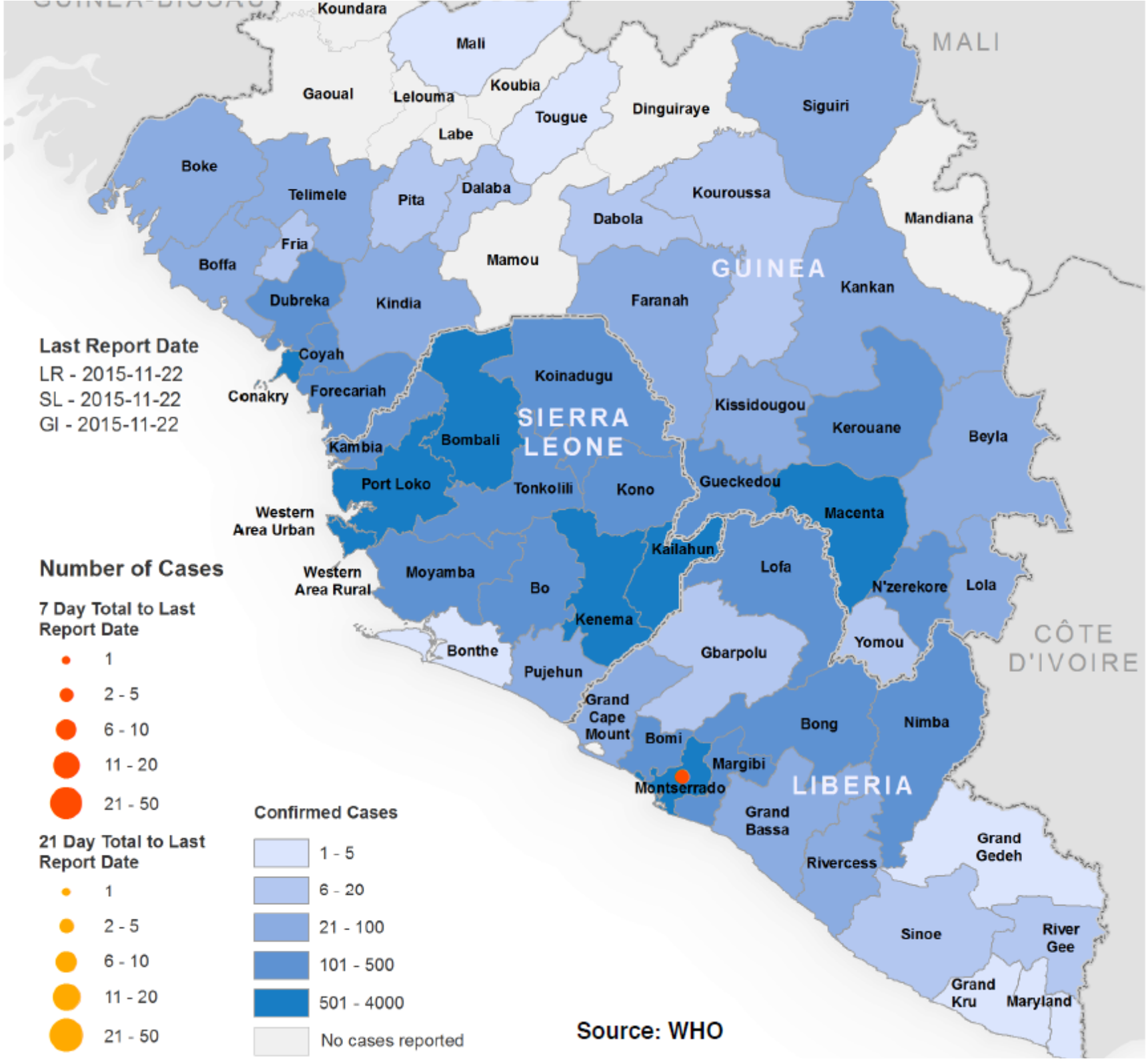


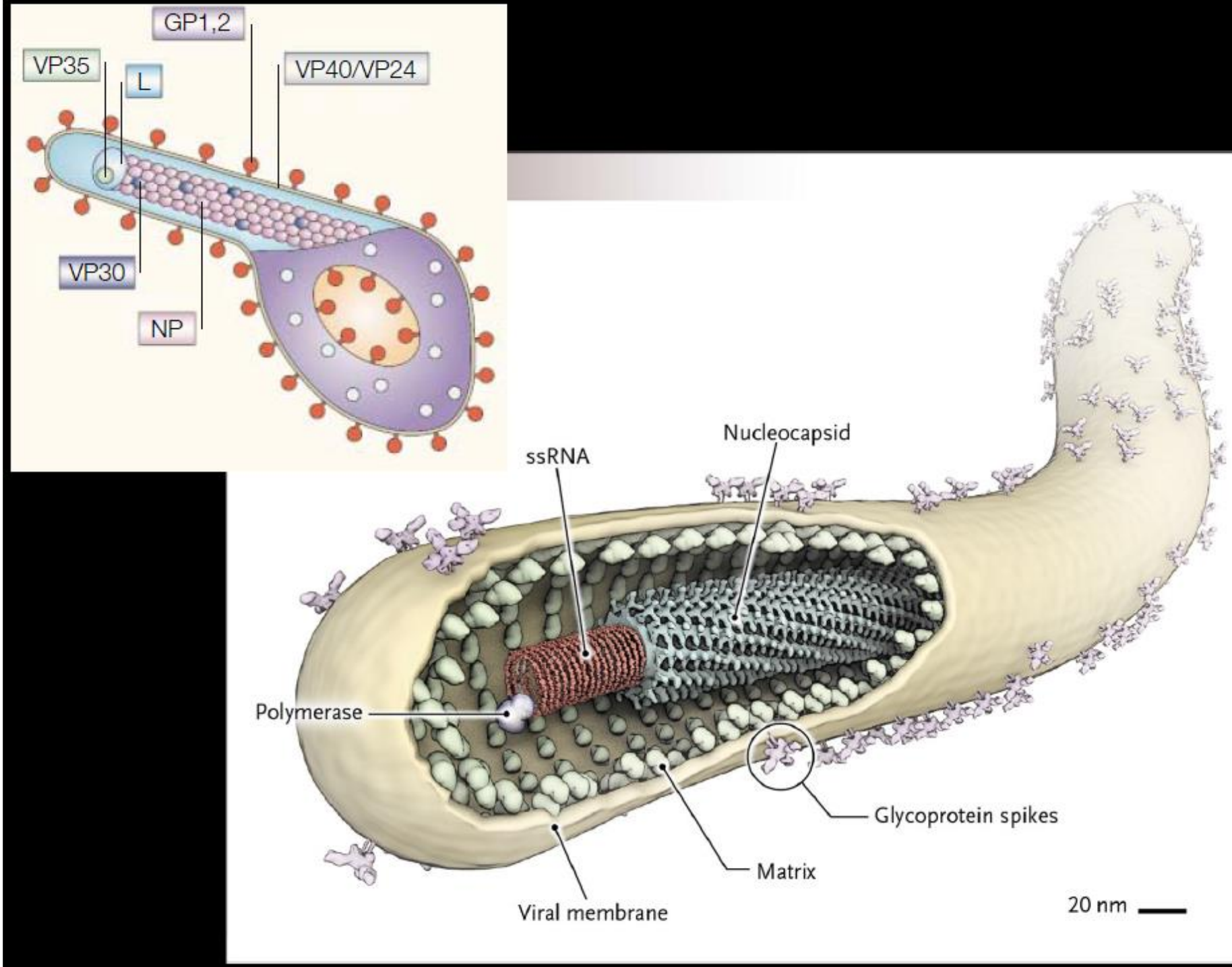
- The Ebola virus belongs to the class of **Filoviruses**
- The family consists of the genera Marburgvirus and Ebolavirus
- Filoviruses consist of a **single-stranded linear RNA** genome
- After entry into the host cell it is transcribed to generate polyadenylated mRNA

- the gene has the following structure:

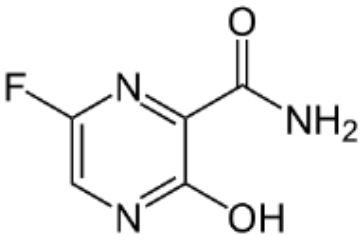


- np (nucleoprotein), virion protein 35, 30,24,40, (vp35,vp40,vp30,vp24), glycoprotein (gp) and polymerase (L)


Koundara
Mali
MALI
Gaoual
Lelouma
Koubia
Tougue
Dinguiraye
Siguiri
Labe
Boke
Telimele
Pita
Dalaba
Kouroussa
Dabola
Mandiana
Fria
Boffa
Mamou
GUINEA
Kankan
Dubreka
Kindia
Faranah
Last Report Date
LR - 2015-11-22
SL - 2015-11-22
GI - 2015-11-22
Coyah
Koinadugu
Conakry
Forecariah
Kissidougou
Kerouane
Beyla
SIERRA LEONE
Kambia
Bombali
Port Loko
Tonkolili
Kono
Gueckedou
Macenta
Western Area Urban
Kailahun
Lofa
Number of Cases
Western Area Rural
Moyamba
Bo
N'zerekore
Lola
7 Day Total to Last Report Date
1
2 - 5
6 - 10
11 - 20
21 - 50
Kenema
Yomou
CÔTE D'IVOIRE
Bonthe
Gbarpolu
Pujehun
Grand Cape Mount
Bong
Nimba
Bomi
Margibi
Montserrado
LIBERIA
Grand Bassa
Grand Gedeh
Rivercess
Confirmed Cases
1 - 5
6 - 20
21 - 100
101 - 500
501 - 4000
No cases reported
21 Day Total to Last Report Date
1
2 - 5
6 - 10
11 - 20
21 - 50
Sinoe
River Gee
Grand Kru
Maryland
Source: WHO


GP1,2
VP35
L
VP40/VP24
VP30
NP
Nucleocapsid
ssRNA
Polymerase
Glycoprotein spikes
Matrix
Viral membrane
20 nm

The development of Ebola drugs



Favipiravir, also known as T-705 or Avigan, is an experimental antiviral drug with activity against many RNA viruses. The mechanism of its actions is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase

The Hepatitis viruses

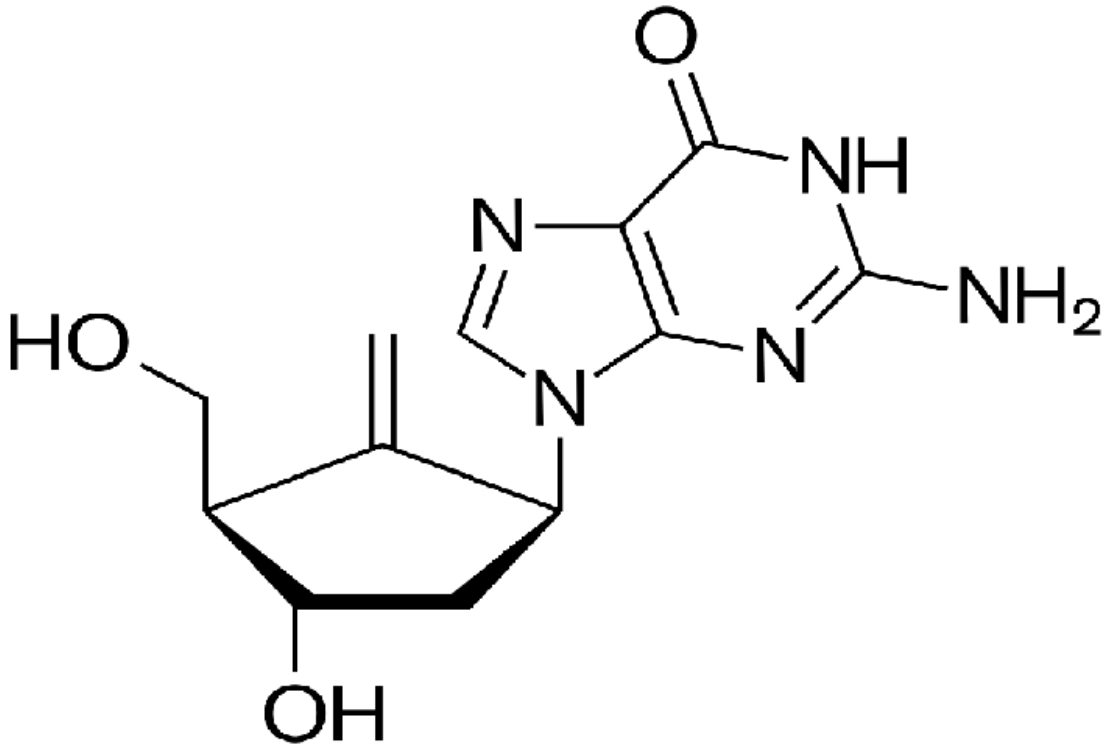
Hepatitis implies injury to liver characterized by presence of inflammatory cells in the liver tissue.

- **Hepatitis A**, (formerly known as infectious hepatitis), is caused by Hepatitis A virus, which is most commonly transmitted by the fecal-oral route via **contaminated food or drinking water**. Every year, approximately 10 million people worldwide are infected with the virus.The Hepatitis virus (HAV) is a Picornavirus; it is non-enveloped and contains a single-stranded RNA packaged in a protein shell.The virus spreads in conditions of poor sanitation and overcrowding.

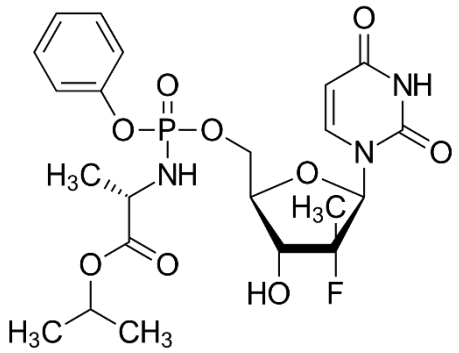
- **Hepatitis B** virus is a DNA virus. Transmission results from exposure to infectious blood or body fluids containing blood. Several vaccines have been developed for the prevention of hepatitis B virus infection. These rely on the use of one of the viral envelope proteins (hepatitis B surface antigen or HBsAg).

- The **hepatitis C** virus (HCV) is spread by blood-to-blood contact. No vaccine against hepatitis C is available. An estimated 150-200 million people worldwide are infected with hepatitis C. Current treatment is a combination of pegylated interferon alpha (brand names Pegasys and PEG-Intron) and the antiviral drug ribavirin.

ENTECAVIR

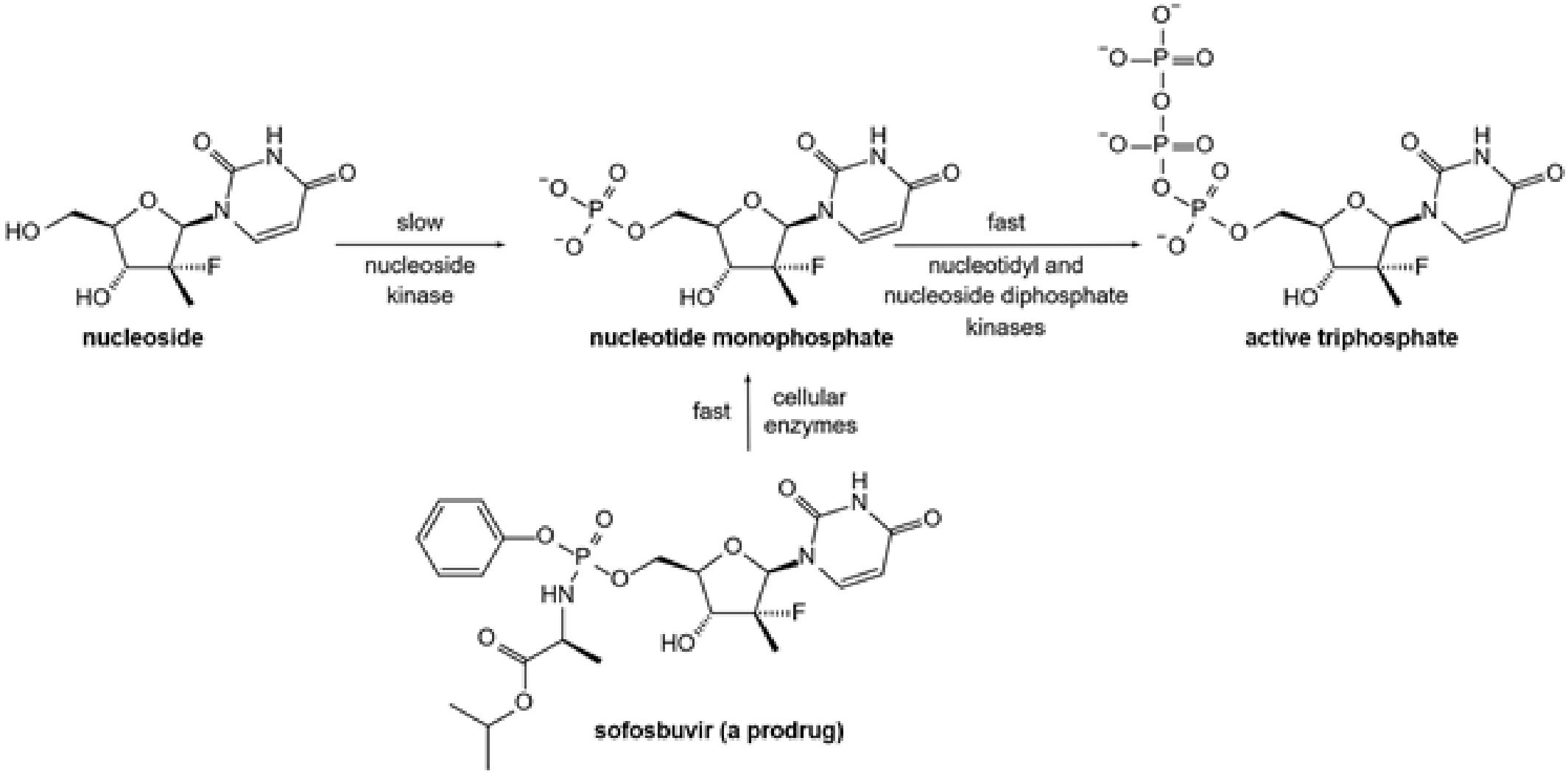


Baraclude, is an antiviral medication used in the treatment of hepatitis B virus (HBV) infection

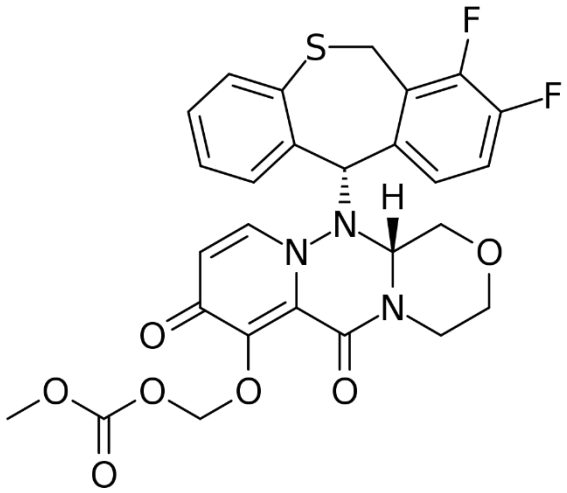


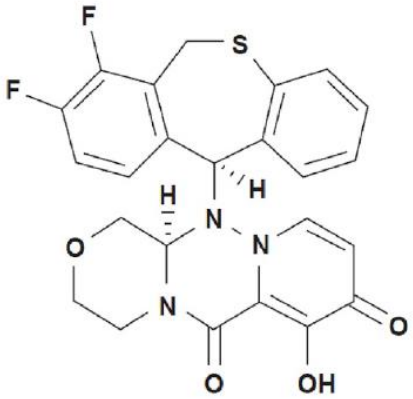
SOFOSBUVIR (HARVONI) 90-mg, 400-mg 28-film-kapli-tablet (Ledipasvir ile)

It is effective against Hepatit C.
Cure rates are 30 to 97% depending on the type of hepatitis C virus involved.
Combined with Ribavirin, interferon, ledipasvir, Velpatasivir.

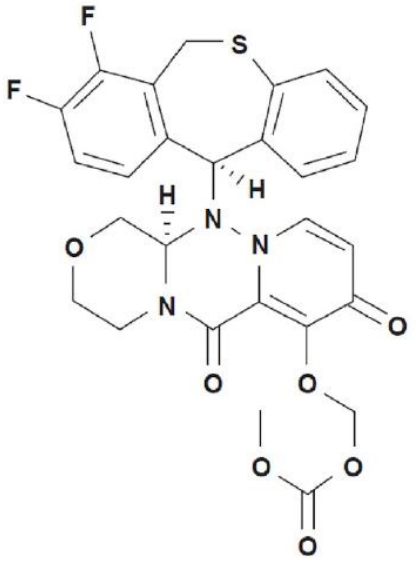

slow
nucleoside
kinase
fast
nucleotidyl and
nucleoside diphosphate
kinases
fast
cellular
enzymes
nucleoside
nucleotide monophosphate
active triphosphate
sofosbuvir (a prodrug)

Baloxavir marboxil [Baloksavir marboksil] XOFLUZA





Baloxavir acid (BXA)



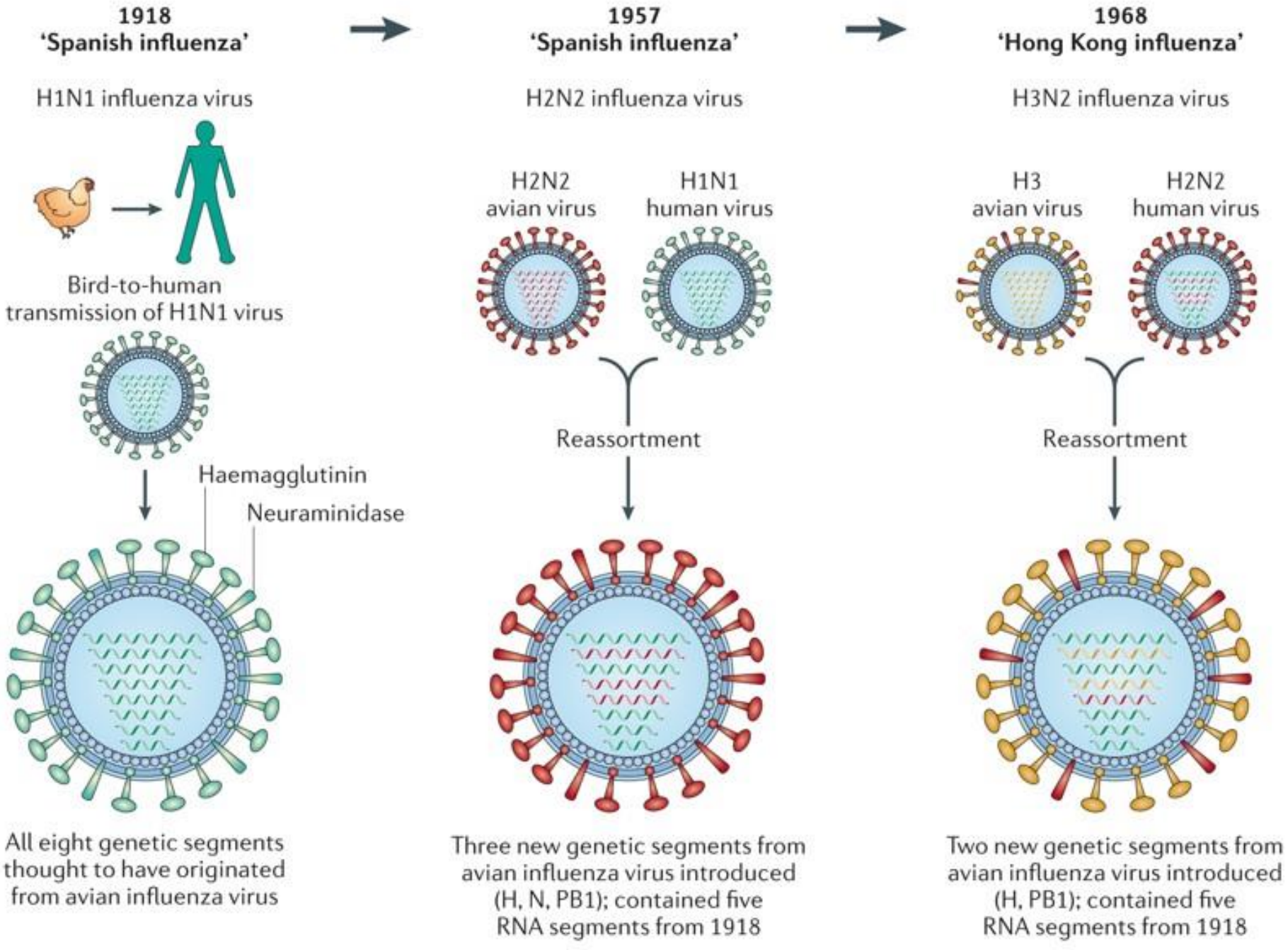
Baloxavir marboxil (BXM)

It is an antiviral medication for treatment of influenza A and influenza B flu.

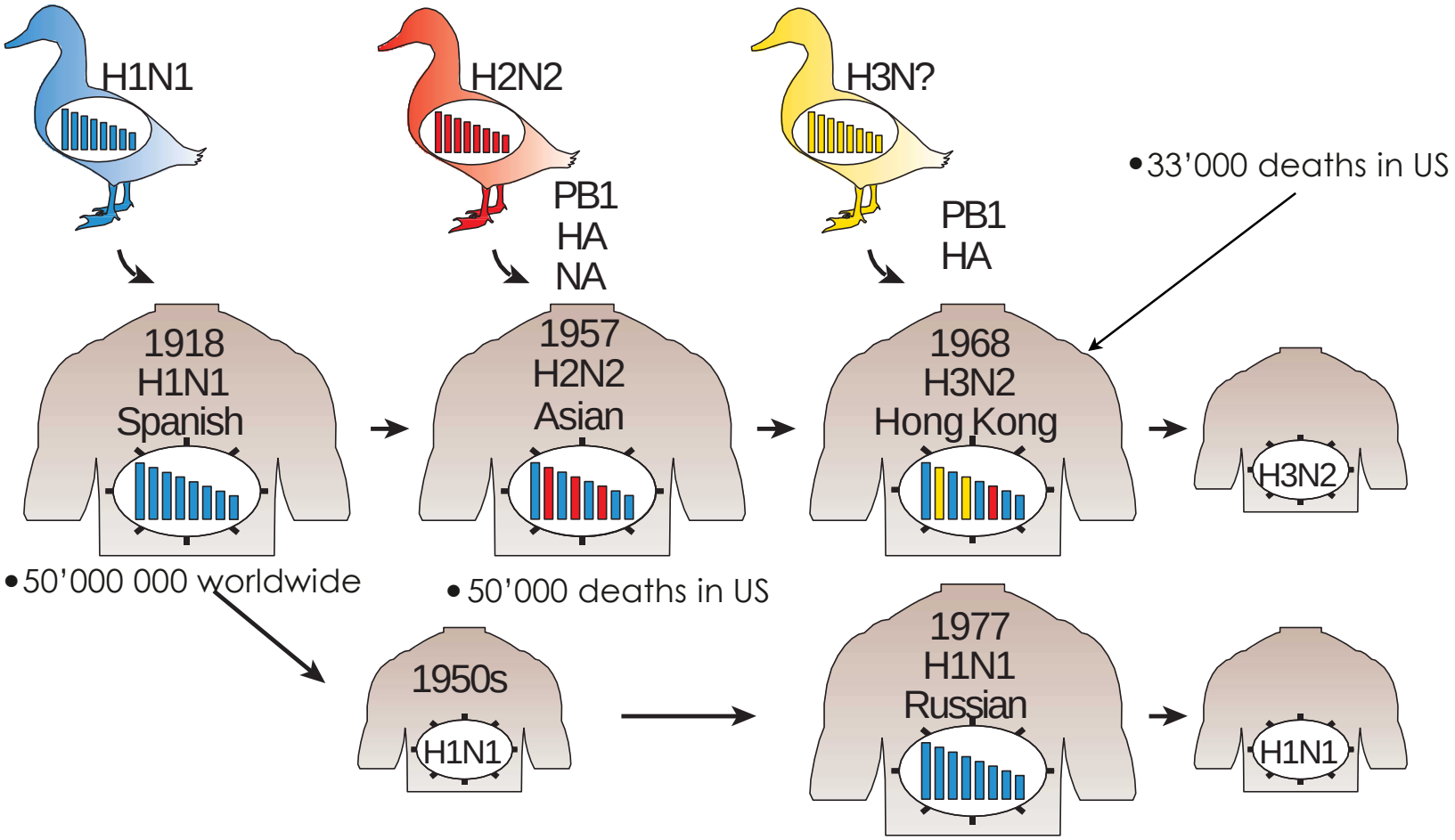
Baloxavir marboxil (BXM) was developed as a prodrug strategy, with its metabolism releasing the active agent, **baloxavir acid** (BXA).
BXA then functions as enzyme inhibitor.

It is taken as a single dose by mouth.

Influenza pandemics

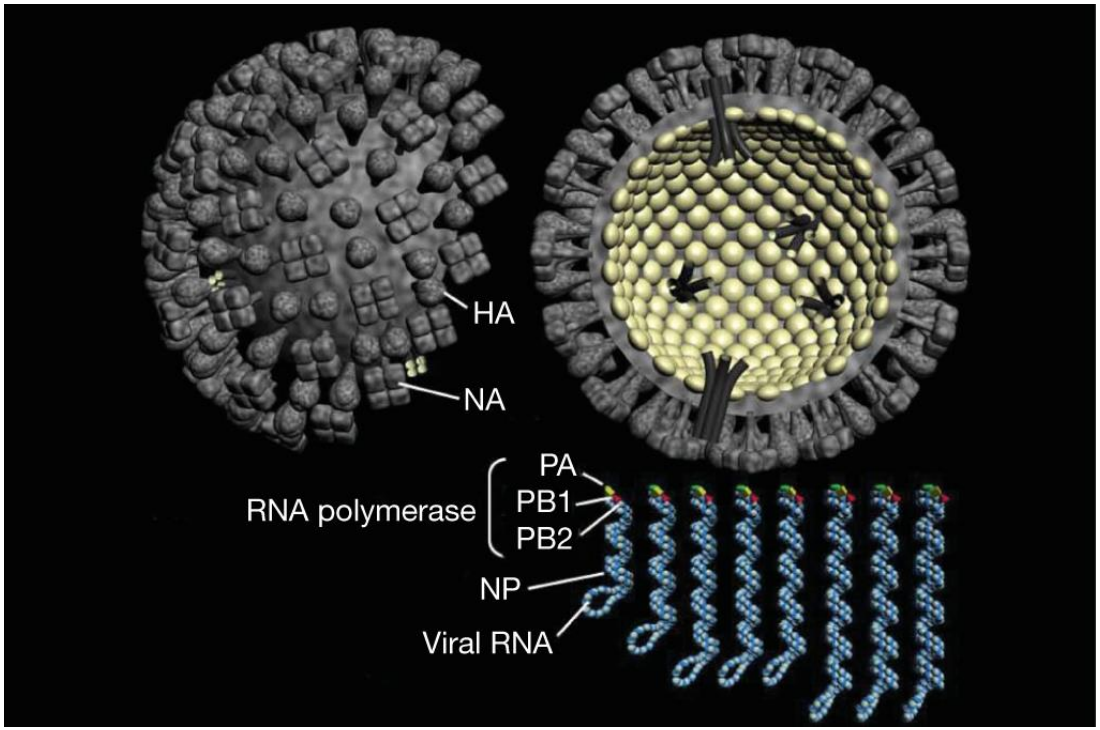


Flu Epidemics

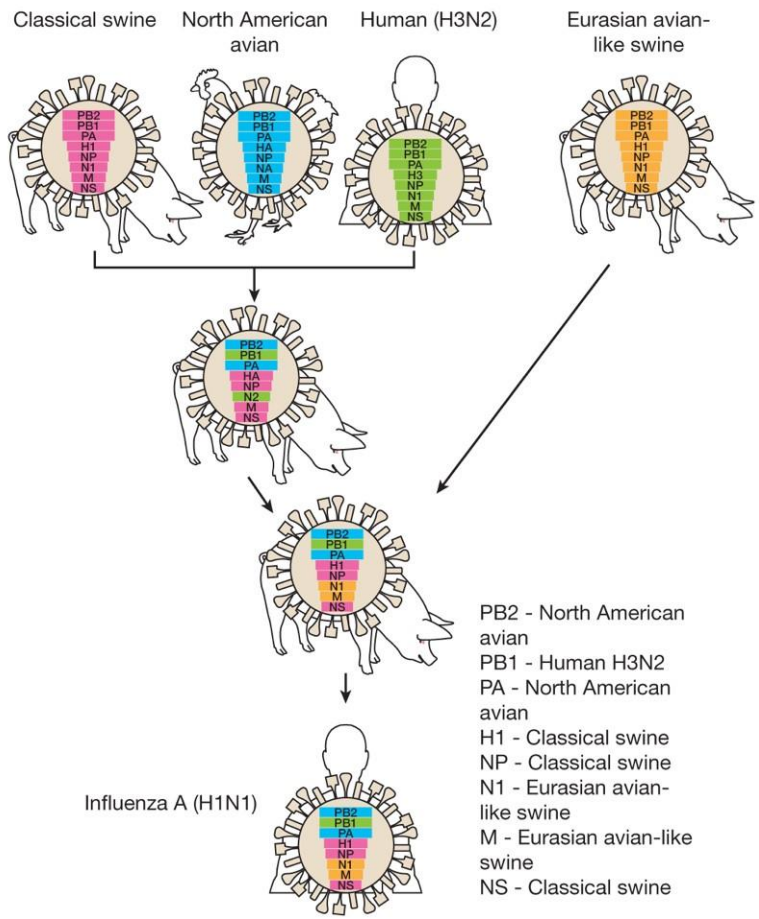


- H5N1 (**bird flu**): originated in Hong Kong 1977, and re-appeared 2003. Highly pathogenic. Severe respiratory infections with high mortality. (261 deaths so far)
- H1N1 (**swine flu**): originated from Mexico

Components of the H1N1 virus



- belongs to the class of influenza A viruses
- genome is composed of eight segments of single-stranded, negative-sense RNA, that each encode 1 or 2 proteins (NP= nucleoprotein; PB components of the polymerase complex)

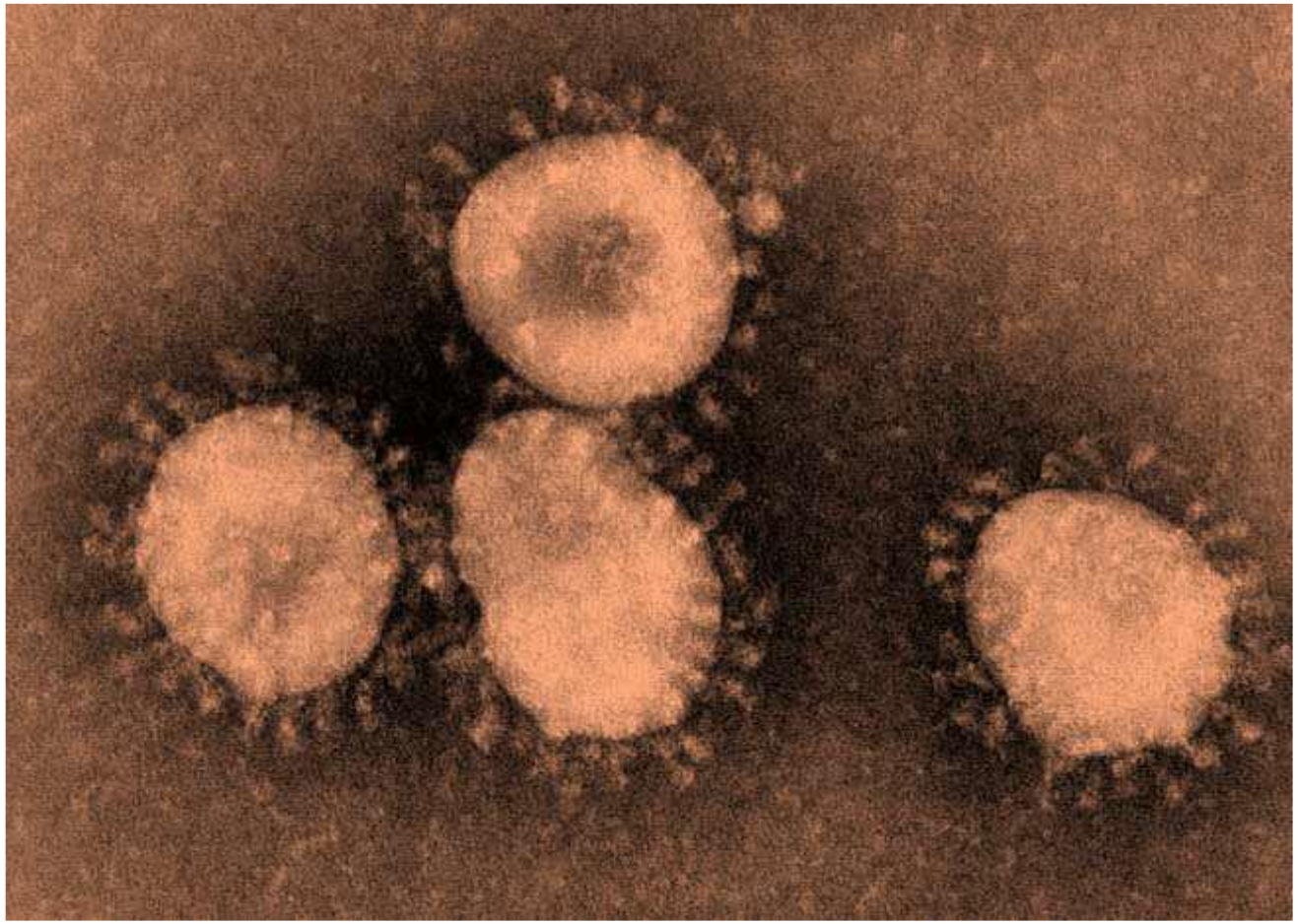


History of the swine flu (2009)

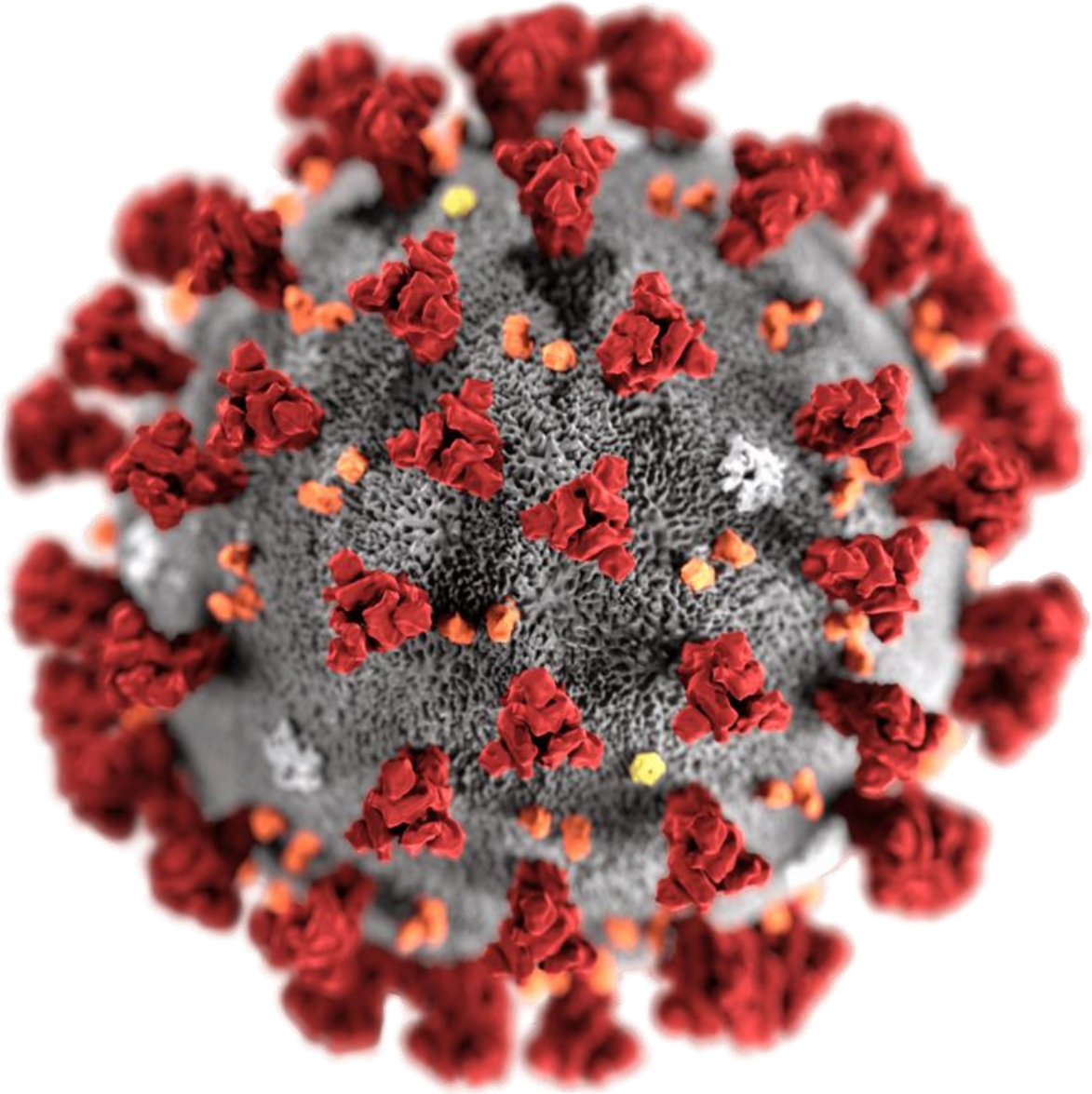
Table I |

Date	Event
Mid-February	Outbreak of respiratory illness in La Gloria, Veracruz, Mexico [31]
12 April	Mexican public health authorities report outbreak in Veracruz to the PAHO
15 April	CDC identifies S-OIVs in the specimen of a boy from San Diego, California
17 April	CDC identifies S-OIVs in the specimen of a girl from Imperial, California
21 April	CDC alerts doctors to a new strain of H 1N1 influenza virus
23 April	The Public Health Agency of Canada identifies S-OIVs in specimens from Mexico
24 April	WHO issues Disease Outbreak Notice
27 April	International spread and clusters of human-to-human transmission prompt WHO to raise the pandemic alert from phase 3 to 4
29 April	WHO raises the pandemic alert from phase 4 to 5 (human-to-human spread in at least two countries in one WHO region)
21 May	41 countries report 11,034 cases, including 85 deaths

CORONA VIRUSES



2019-nCoV – Wuhan coronavirus



The 2019 novel coronavirus (provisionally named 2019-nCoV) informally known as the Wuhan coronavirus, is a contagious virus that causes 2019-nCoV acute respiratory disease, a respiratory infection.

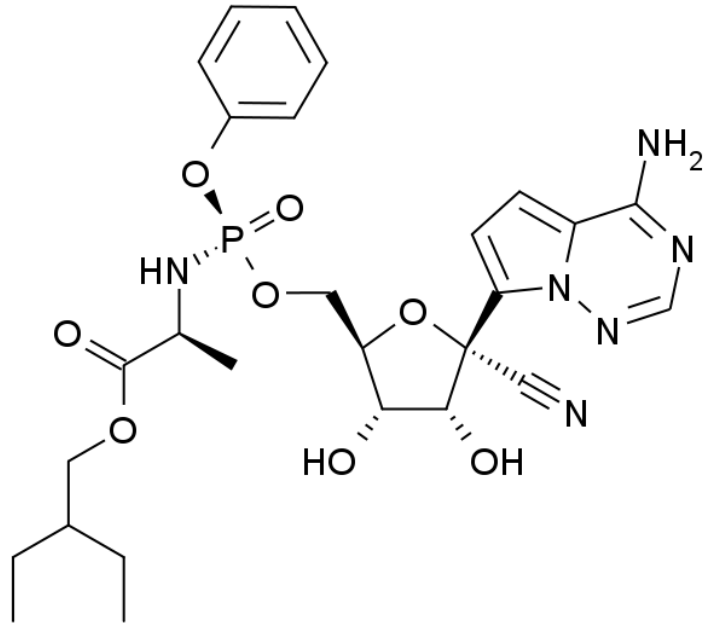
It is the cause of the ongoing 2019–20 Wuhan coronavirus outbreak, a global health emergency.

Genomic sequencing has shown that it is a positive-sense, single-stranded RNA coronavirus.

Coronaviruses has the affinity of Angiotensin converting enzyme 2 (ACE2) in lungs, make interaction with this enzyme and enter the cell

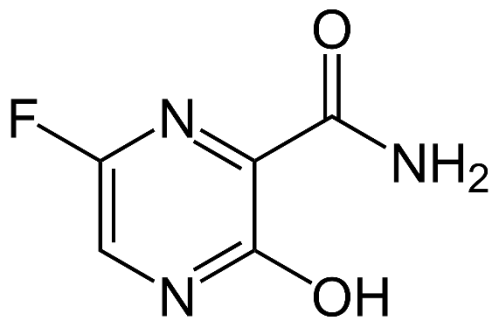
Your higher number of ACE 2 receptors means that the better the chances of viruses getting involved in their cells.

Remdesivir Gilead



Remdesivir is a novel antiviral drug in the class of nucleotide analogs. It was developed by Gilead Sciences as a treatment for Ebola virus disease. It subsequently was found to show antiviral activity against other single stranded RNA viruses such as coronaviruses the (including MERS and SARS viruses)

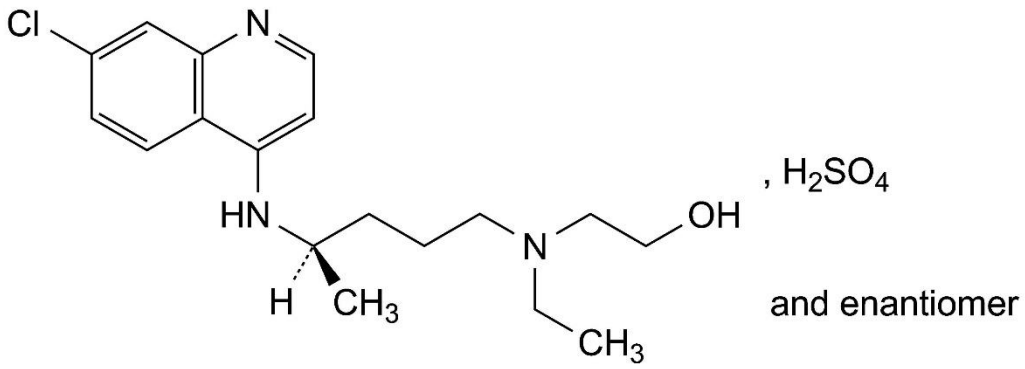
Favipiravir (Avigan) :



6-Fluoro-3-hydroxy-2-pyrazincarboxamide

Favipiravir, (=favilavir) is an antiviral drug being developed by Toyama Chemical (Fujifilm group) of Japan with activity against many RNA viruses. It has shown activity against influenza viruses, West Nile virus, yellow fever virus, foot-and-mouth disease virus as well as other flaviviruses

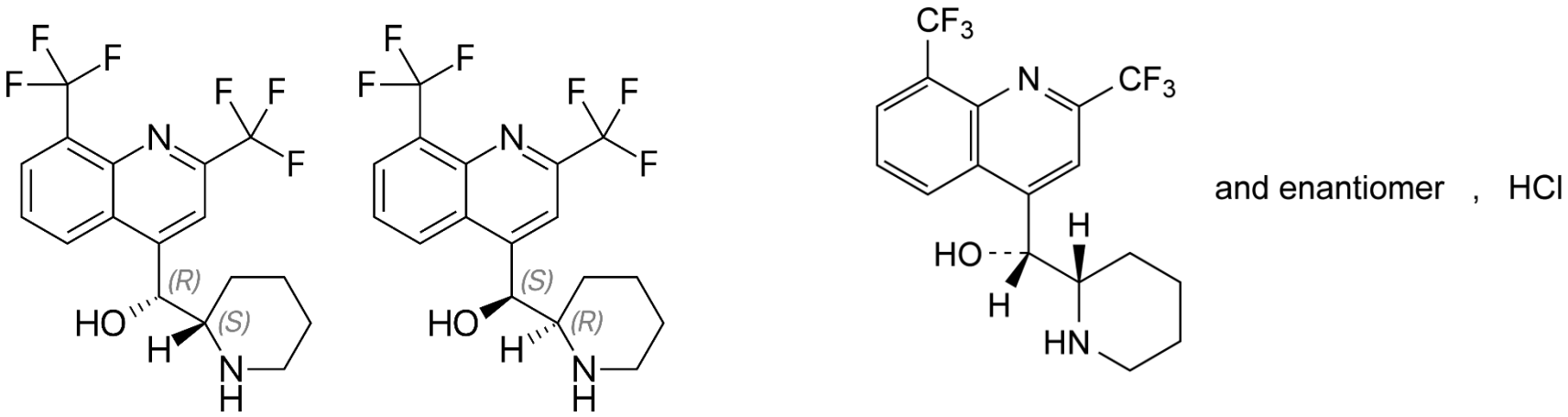
Hydroxychloroquine **PLAQUENIL**



2-[[(4*RS*)-4-[(7-Chloroquinolin-4-yl)amino]pentyl]-(ethyl)amino]ethan-1-ol sulfate.

Hydroxychloroquine (HCQ), is used to prevent and treat malaria. Other uses include treatment of rheumatoid arthritis, lupus. It is also being studied as an experimental treatment for coronavirus disease 2019 (COVID-19).

Mefloquine HCl



(*RS*)-[2,8-Bis(trifluoromethyl)quinolin-4-yl][(2*SR*)-piperidin-2-yl]methanol hydrochloride

Mefloquine, sold under the brand names **Lariam**. It can be used to treat mild or moderate malaria but is not recommended for severe malaria.