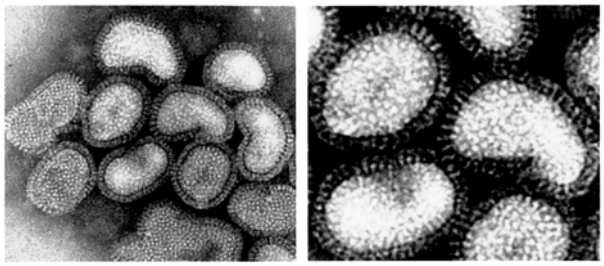
INFLUENZA VIRUS

Adapté en partie des exposés de la Chaire Franqui 2003
"Antiviral drugs and Discoveries in Medicine"
Prof. E. De Clercq, KU-Leuven
http://www.md.ucl.ac.be/chaire-francqui/

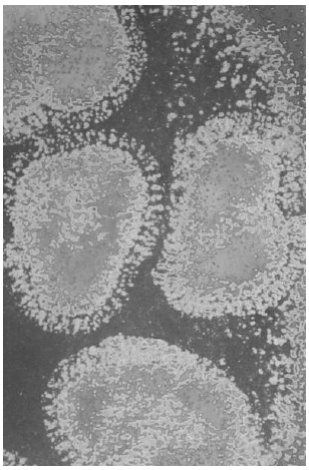
Influenza virus



Electron micrographs of purified influenza virions. Hemagglutinin (HA) and neuraminidase (NA) can be seen on the envelope of viral particles. Ribonucleoproteins (RNPs) are located inside the virions.

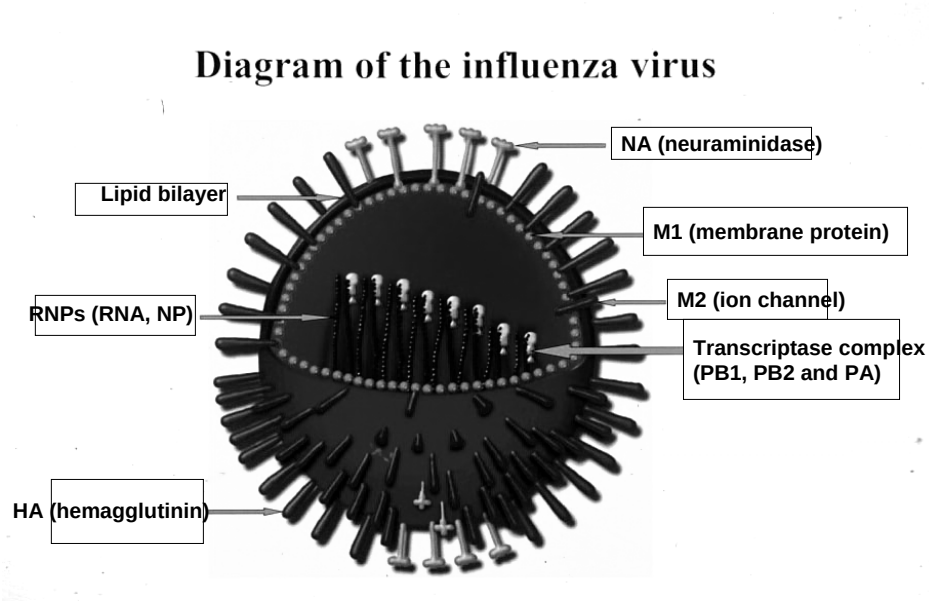
http://www.virology.net/Big_Virology/BVRNAortho.html

Influenza

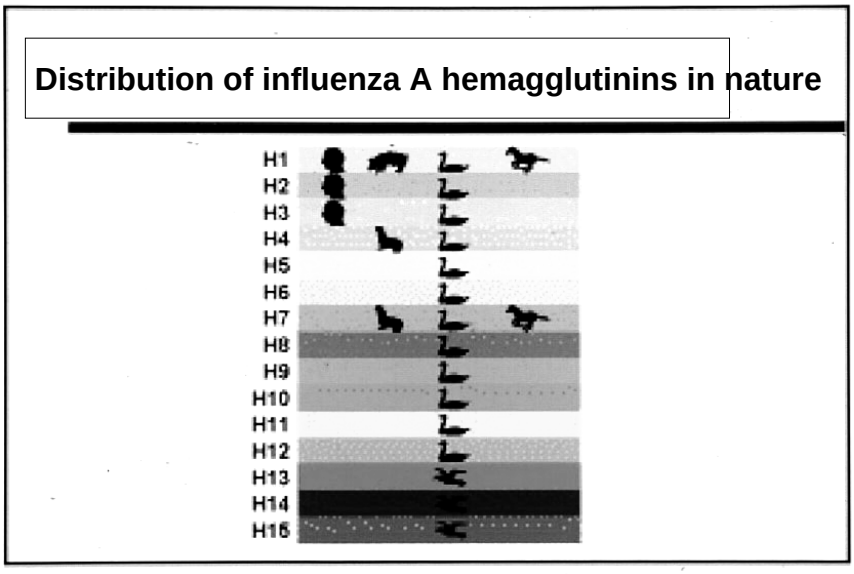


Layne *et al*., Science 293: 1729 (2001)

Diagram of the influenza virus

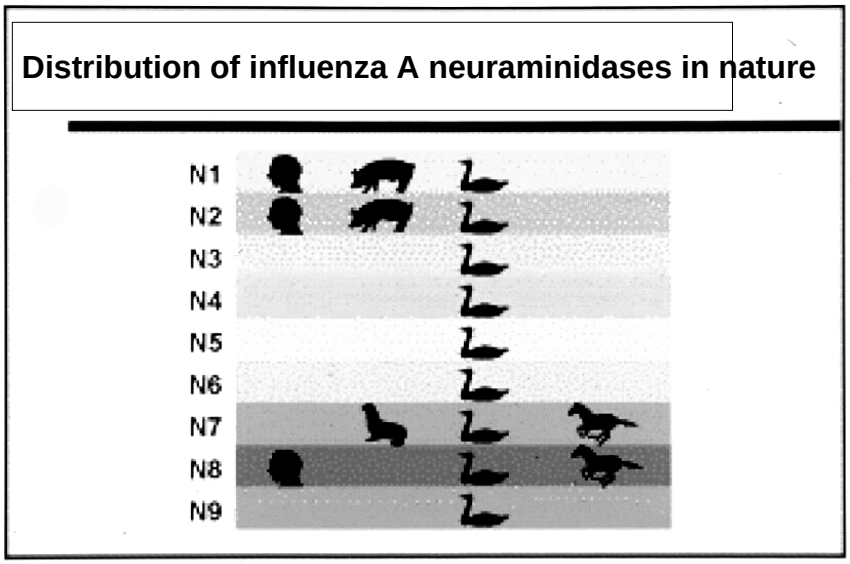


Distribution of influenza A hemagglutinins in nature

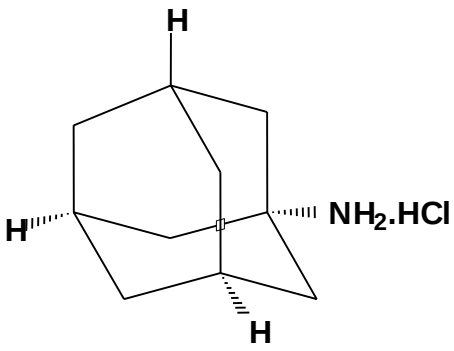


http://www.brown.edu/Courses/Bio_160/Projects1999/flu/mechanism.html

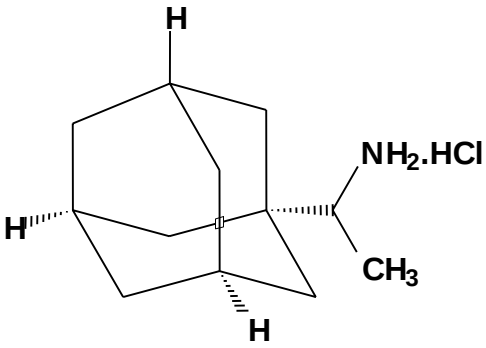
Distribution of influenza A neuraminidases in nature



http://www.brown.edu/Courses/Bio_160/Projects1999/flu/mechanism.html

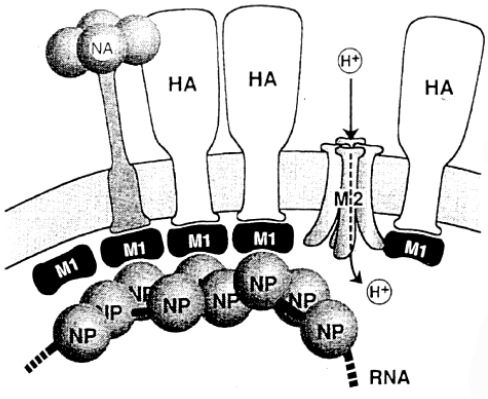


Amantadine

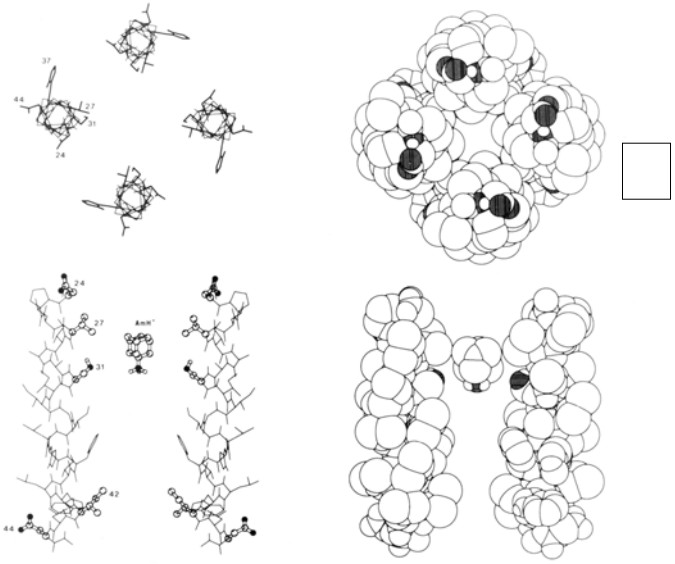


Rimantadine

Amantadine/rimantadine:
mechanism of action limited to influenza A viruses



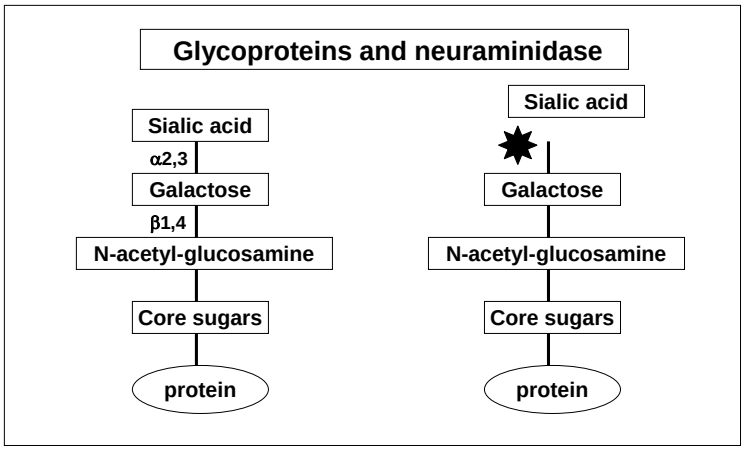
The tetrameric M2 helix bundle



Sansom & Kerr, Protein Eng. 6: 65-74 (1993)

Neuraminidase (NA):

Cleaves sialic acid from cell-surface glycoprotein

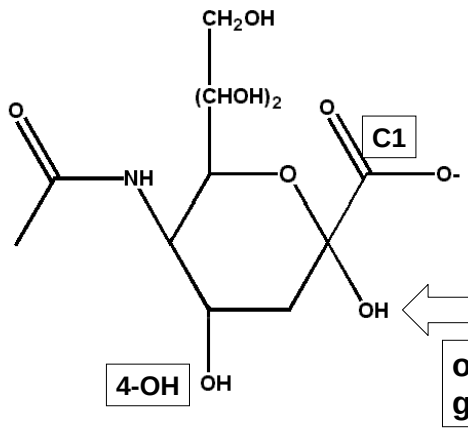


Influenza virus neuraminidase

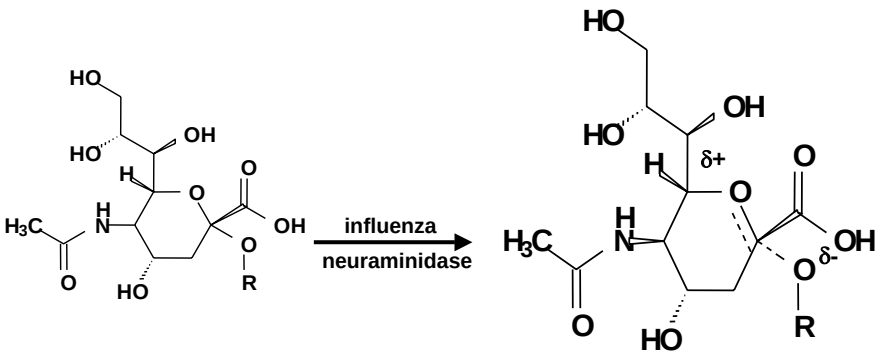
Functions:

- **removes terminal sialic acid residues**
- **promotes release of virus particles from the cells**
- **destroys cellular receptors recognized by hemagglutinin**
- **prevents virus aggregation at the cell surface**
- **prevents viral inactivation by respiratory mucus**

Sialic acid...



osidic linkage with galactose (2 → 3)

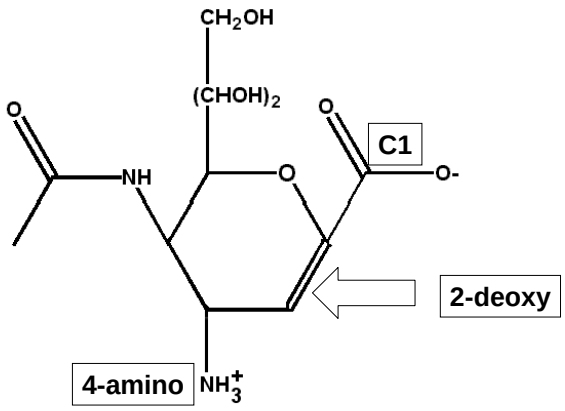


Sialyl α-glycoside
R = glycoprotein

Transition state

Abdel-Magid *et al*., Curr. Opin. Drug Discov. Dev. 4: 776-791 (2001)

First inhibitor of neuraminidase… (1969)



2,4-dideoxy-2,3-didehydro-4-amino-D-*N-acetylneuraminic acid*

Meindl et al., Hoppe-Seyler's Z. Physiol. Chem., 350:1088-1092, 1969

From 1969 to 1993...

- **2,3-dideoxy-2,3-didehydro-4-amino-D-*N*-acetylneuraminic acid**
  K_i ~ 0.01 mM vs K_m for sialic acid ~ 1mM

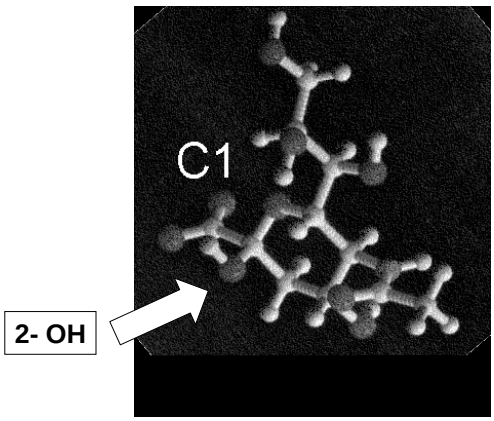
  ⇒ **does not work...**

- **1983: structure of neuraminidase at 2.9 Å resolution**
  several residues at catalytic site are constant
  antigenic sites are highly variable…

  (Colman et al., Nature 303:41-44, 1983)

  ⇒ **Can you visualize the catalytic site ?**

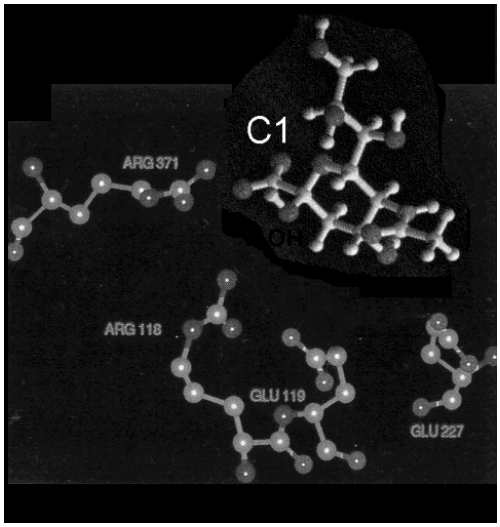
From sialic acid to zanamivir… (1)



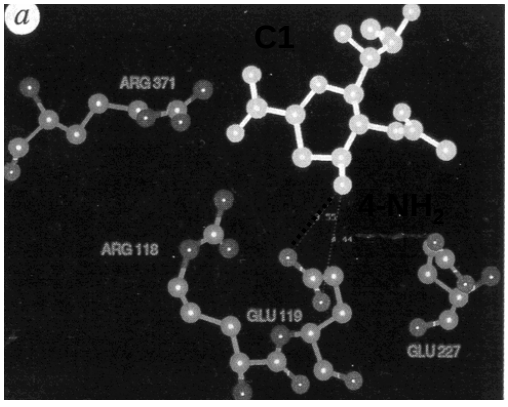
acide sialique ou N-acétyl-neuraminique

Dfrom sialic acid to zanamivir… (2)

sialic acid binds through its C1 carboxylate to Arg 371



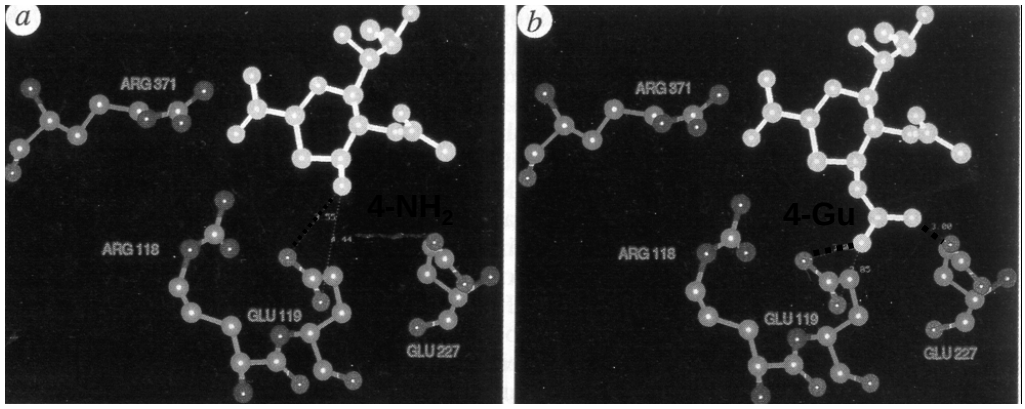
From sialic acid to zanamivir… (3)



4-deoxy-4-amino ...

résidues 119 et 227 are highly conserved...

From sialic acid to zanamivir… (4)



4-deoxy-4-amino ...

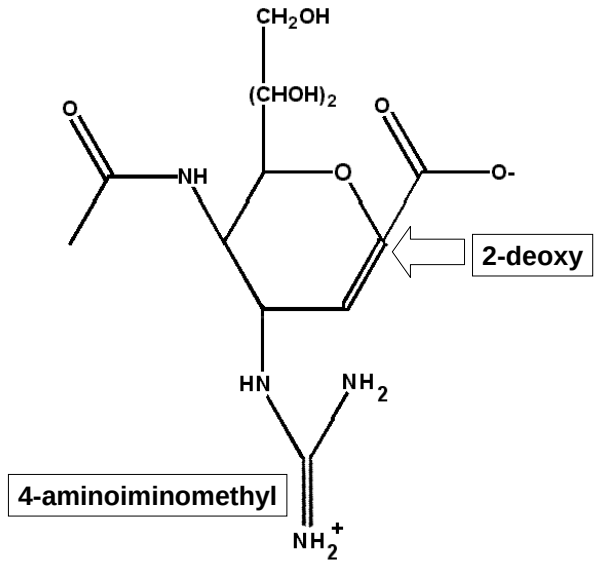
4-deoxy-4guanidino...

both residues 119 and 227 are now involved and 199 is much closer….

Zanamivir...
(1993)

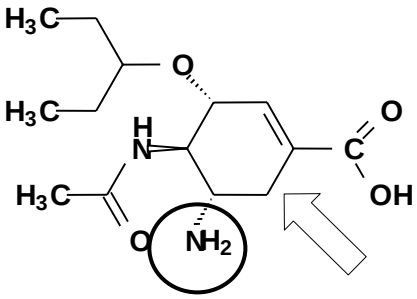
2,4-dideoxy-2,3-didehydro-4-guanidino-D-*N-acetylneuraminic acid*

von Itzstein et al.,
Nature 363: 418-423, 1993

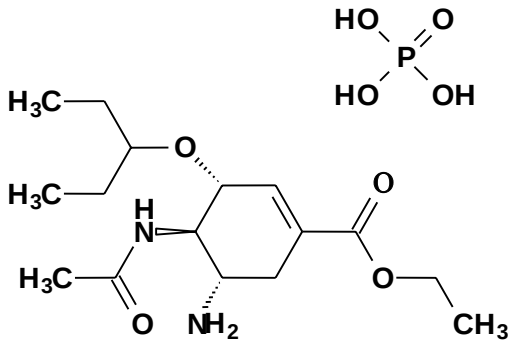


Zanamivir

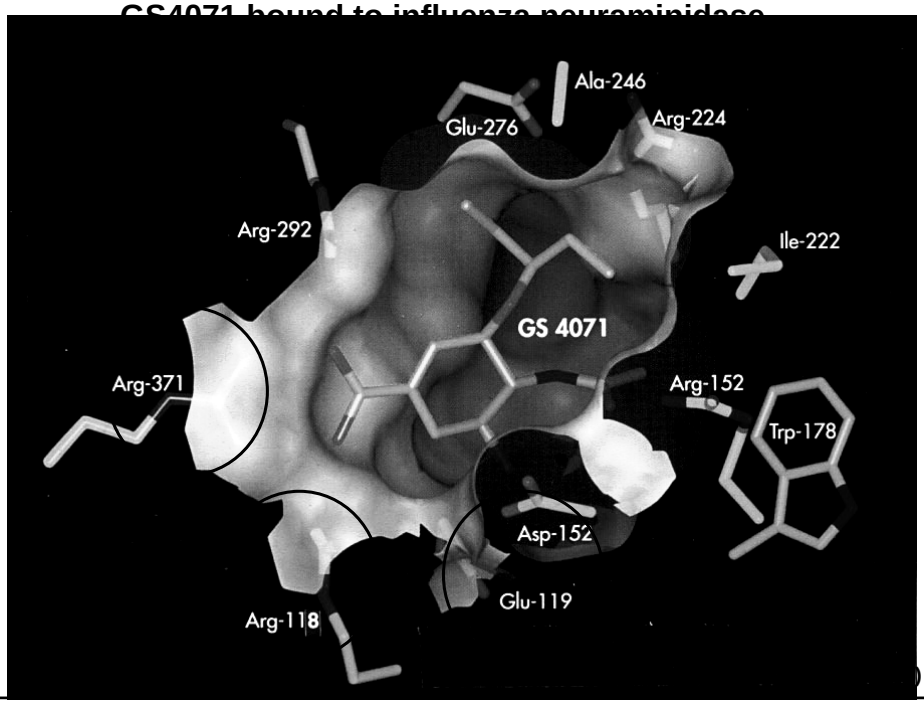
- active against both influenza A and B
- IC_{50} : 0.21-2.6 ng/ml for influenza neuraminidase
- efficacy demonstrated in mouse and ferret models for influenza (upon topical administration)
- has to be administered by inhalation : 10 mg bid
- therapeutically effective (5 days) : significant reduction in duration of illness
- prophylactically effective (4 weeks) : significant reduction in number of ill subjects
- well tolerated : clinical adverse events not different from placebo
- no evidence for emergence of drug-resistant virus



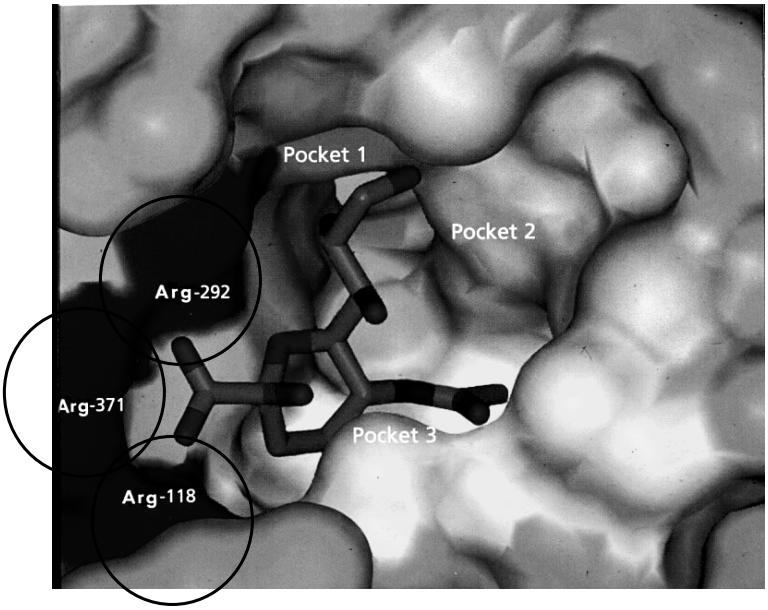
GS4071



Oseltamivir phosphate



GS4071 bound to influenza neuraminidase



Oseltamivir

- active against both influenza A and B
- IC_{50} : < 1 ng/ml for influenza neuraminidase
- efficacy demonstrated in mouse and ferret models for influenza (upon oral administration)
- can be administered orally : 75 or 150 mg bid
- therapeutically effective (5 days) : significant reduction in duration of illness
- prophylactically effective (6 weeks) : significant reduction in number of ill subjects
- well tolerated : clinical adverse events not different from placebo
- no evidence for emergence of drug-resistant virus

RESISTANCE MUTATIONS TO NEURAMINIDASE INHIBITORS

Neuraminidase

119 Glu → Gly:

- **specific for zanamivir;**
- **Glu 119 interacts with guanidinium group of zanamivir**

292 Arg → Lys:

- **found for zanamivir; cross-resistance to oseltamivir**
- **Arg 292 interacts with carboxylic acid group of zanamivir and oseltamivir**

Hemagglutinin

Some mutations (i.e. 198 Thr → Ile) diminish affinity of hemagglutinin for its receptor

McKimm-Breschkin, Antiviral Res. 47: 1-17 (2000)

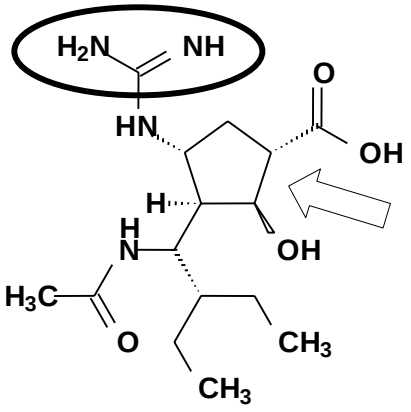
Benefits offered by neuraminidase inhibitors

Therapeutically:

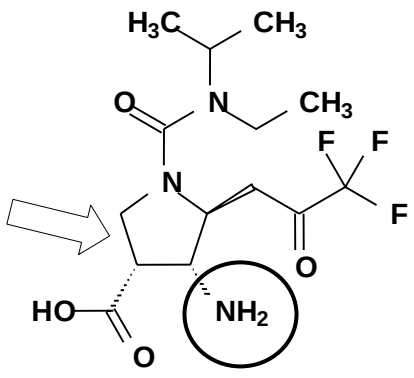
- **Reduction in illness duration by 1-2 days**
- **Reduction in risk-virus transmission to household or healthcare contacts**
- **Reduction in complications (sinusitis, bronchitis)**
- **Reduction in use of antibiotics**

Prophylactically:

- **Seasonal prevention of infection**



RWJ-270201

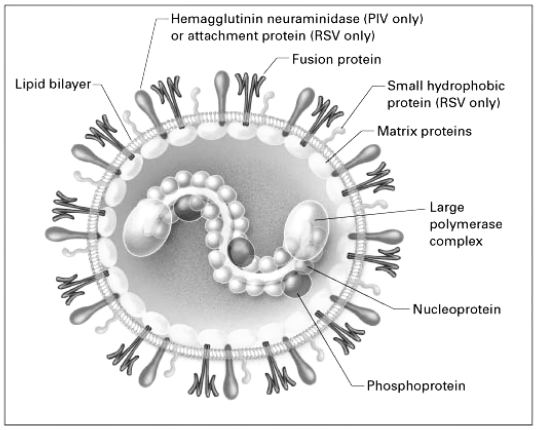


Wang *et al*., J. Med. Chem. 44: 1192-1201 (2001)

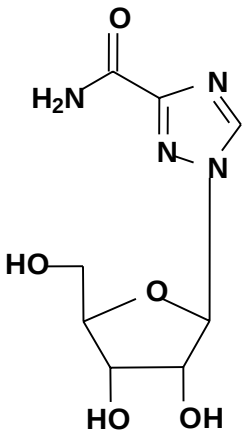
Smee *et al*., Antimicrob. Agents Chemother. 45: 743-748 (2001)
Sidwell *et al*., Antimicrob. Agents Chemother. 45: 749-757 (2001)

RESPIRATORY SYNCYTIAL VIRUS (RSV)

Respiratory Syncytial Virus (RSV) and Parainfluenza Virus (PIV)



Hall, N. Engl. J. Med. 344: 1917-1928 (2001)



Ribavirin

Virazole®

APPROVED ANTIVIRAL DRUGS FOR THE TREATMENT OF THE MAJOR RESPIRATORY TRACT VIRUS INFECTIONS in 2003

Adenoviruses : none

Picornaviruses

Entero : none

Rhino : none

Orthomyxoviruses

Influenza : Neuraminidase inhibitors: zanamivir, oseltamivir

: Amantadine and rimantadine (for influenza A only)

Paramyxoviruses

Parainfluenza : none

Respiratory syncytial virus : Ribavirin

SARS virus : none