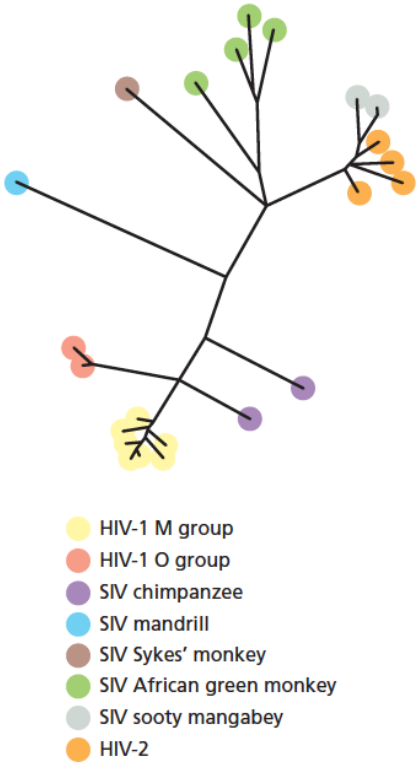
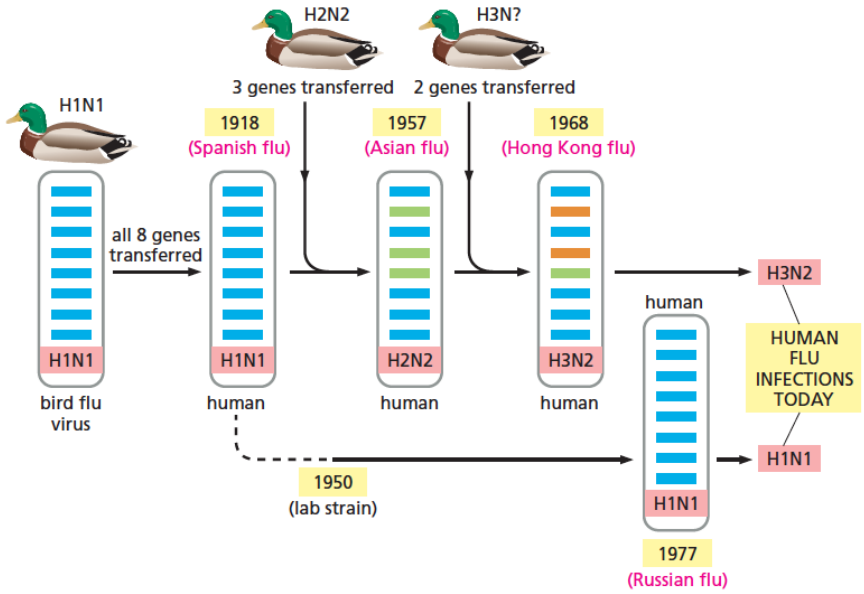
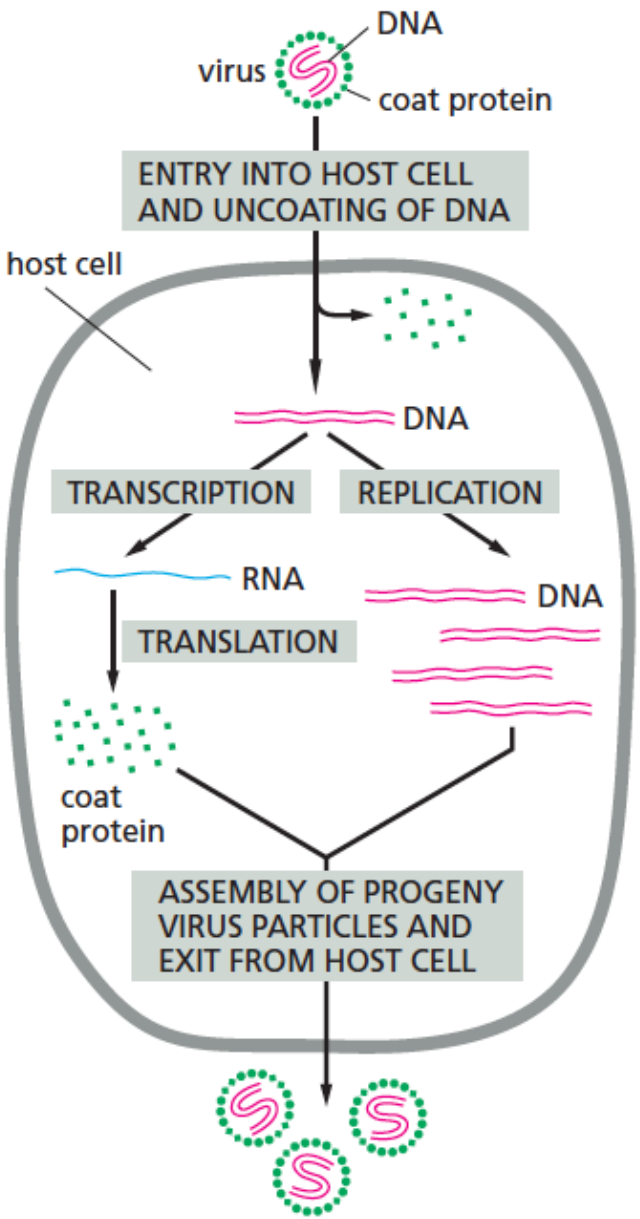
Basic Biology of Viruses and Pharmaceutical Development of Antiviral Medication and Other Treatments



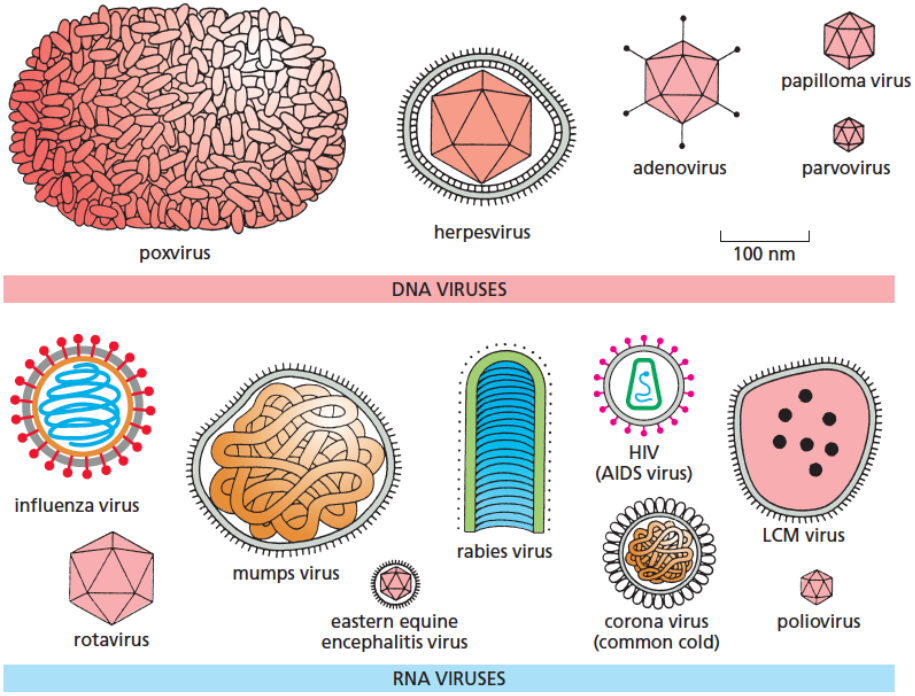


Mark Vander Wal
MacMillan Group Meeting
February 23, 2012

Introduction: Basics of Viruses and the Viral Life Cycle

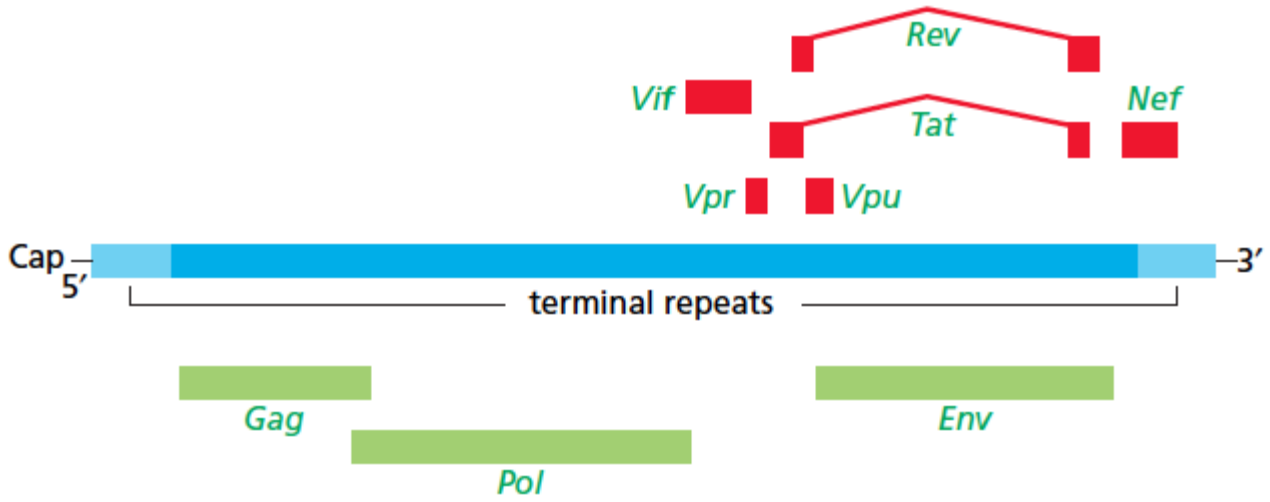


- Viruses are simplest form of biological "life" known
- Viral life cycle depends entirely on interaction with host cells
- All viruses contain genetic information in the form of either DNA or RNA which can be single or double stranded
- The genetic information of a virus is contained in a protein coat
- Some, but not all viruses, have a lipid bilayer surrounding the protein coat



Introduction: Basics of Viruses and the Viral Life Cycle

- All viral genomes encode for three types of proteins: HIV an illustrative example

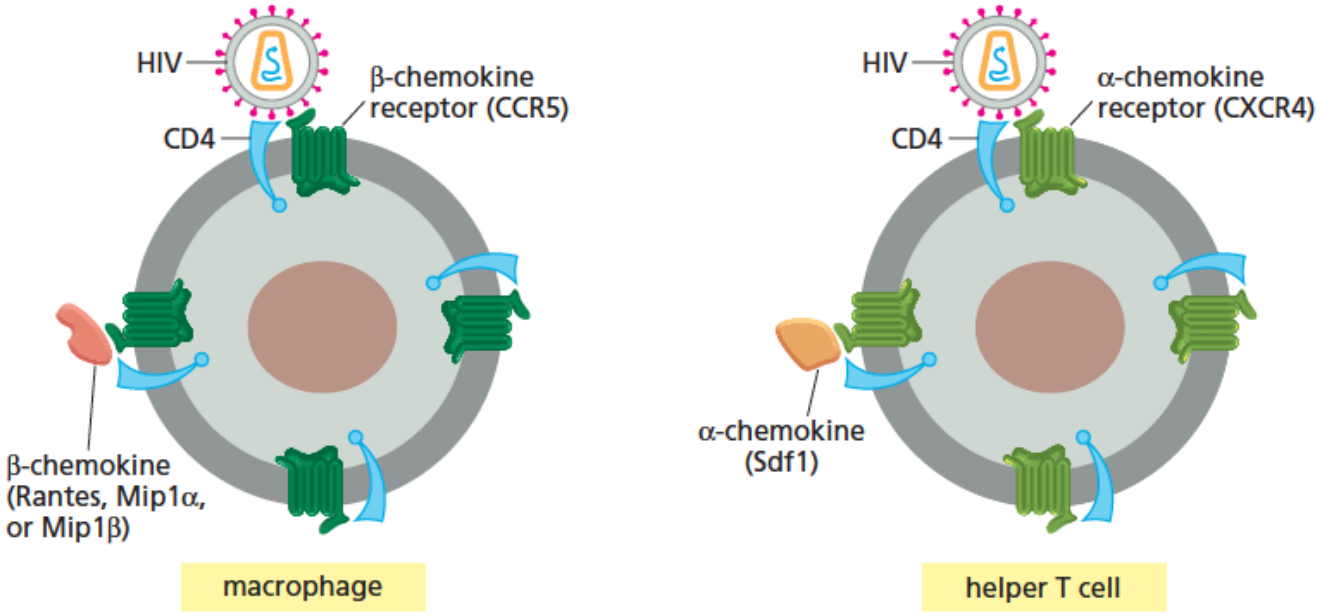


- All viruses encode genes for replication machinery, capsid proteins, and host cell modification
- Retroviruses, like HIV, encode three basic genes Gag (capsid proteins), Pol (reverse transcriptase and integrase), and Env (envelope proteins)
- HIV has an unusually complex genome as it contains six additional genes that modify normal host cell function

Molecular Biology of the Cell 5th Ed.; Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

Introduction: Basics of Viruses and the Viral Life Cycle

- First stage of viral life cycle involves infiltration of desired host cell

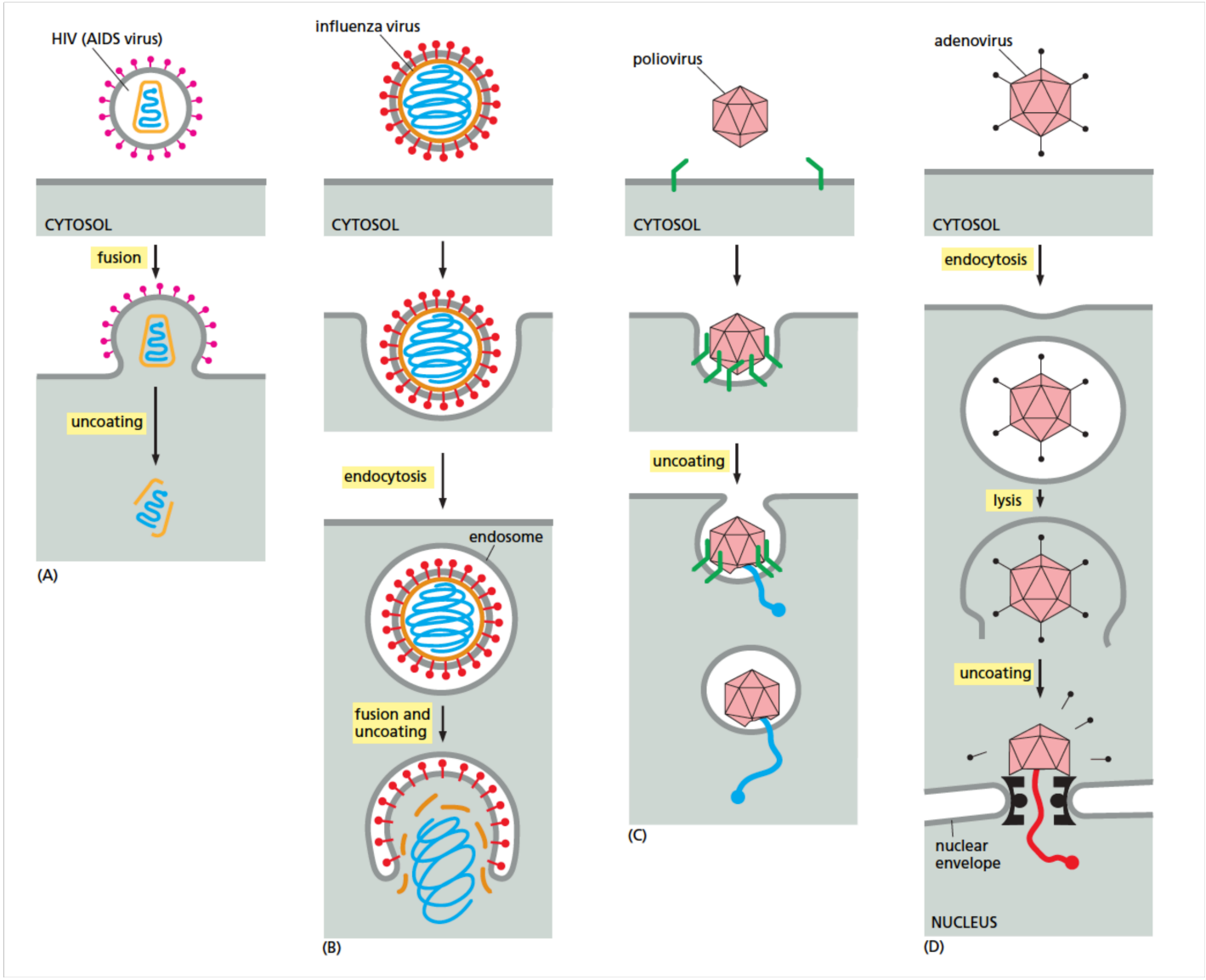


- Viruses bind to cell membrane molecules (often proteins) of host cells as recognition binders for viral surface proteins
- This recognition is key for the virus' ability to infect the desired cell type in host
- For HIV a primary binder (CD4) and a co-binder (either CCR5 or CXCR4) are required

Molecular Biology of the Cell 5th Ed.; Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

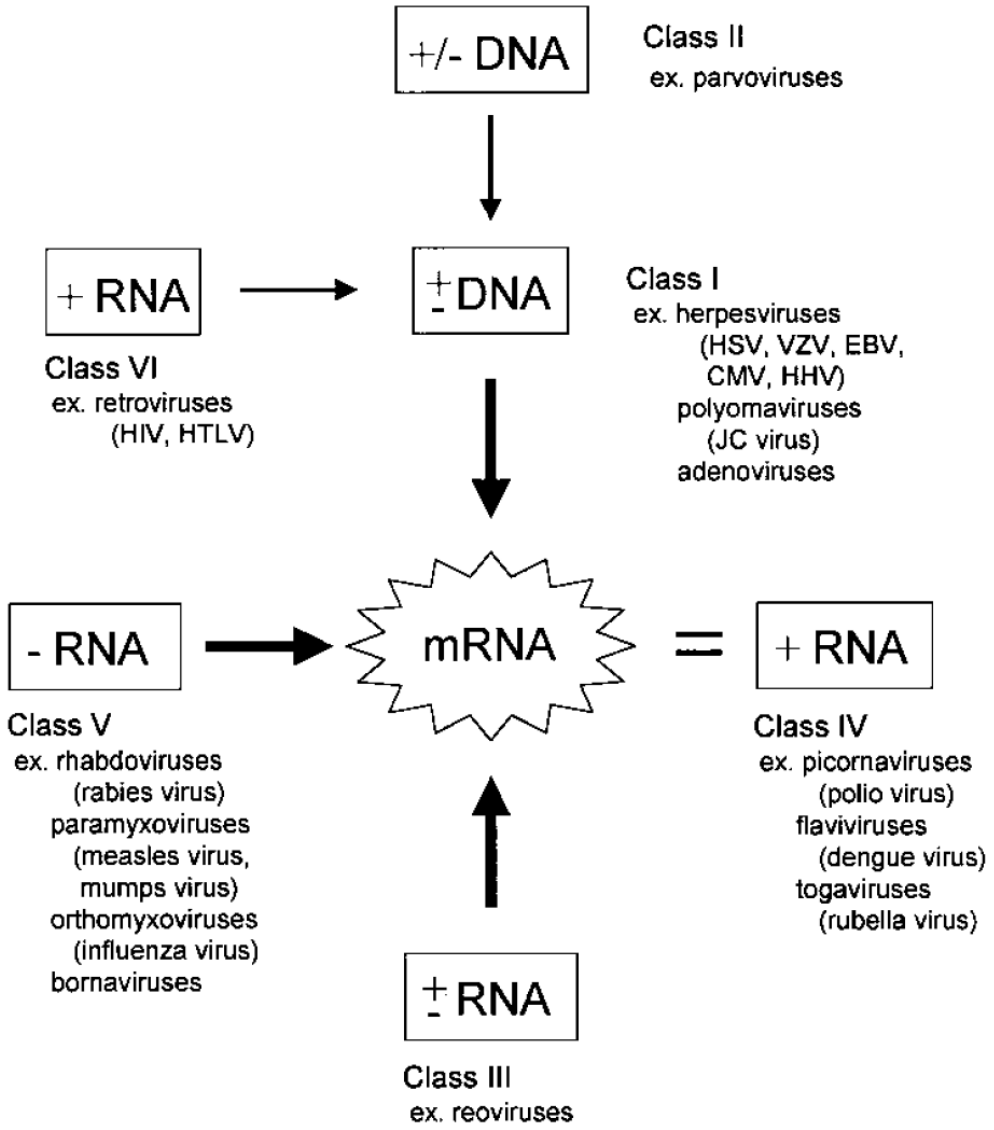
Introduction: Basics of Viruses and the Viral Life Cycle

- Several strategies exist for viral entry and release of genome



Introduction: Basics of Viruses and the Viral Life Cycle

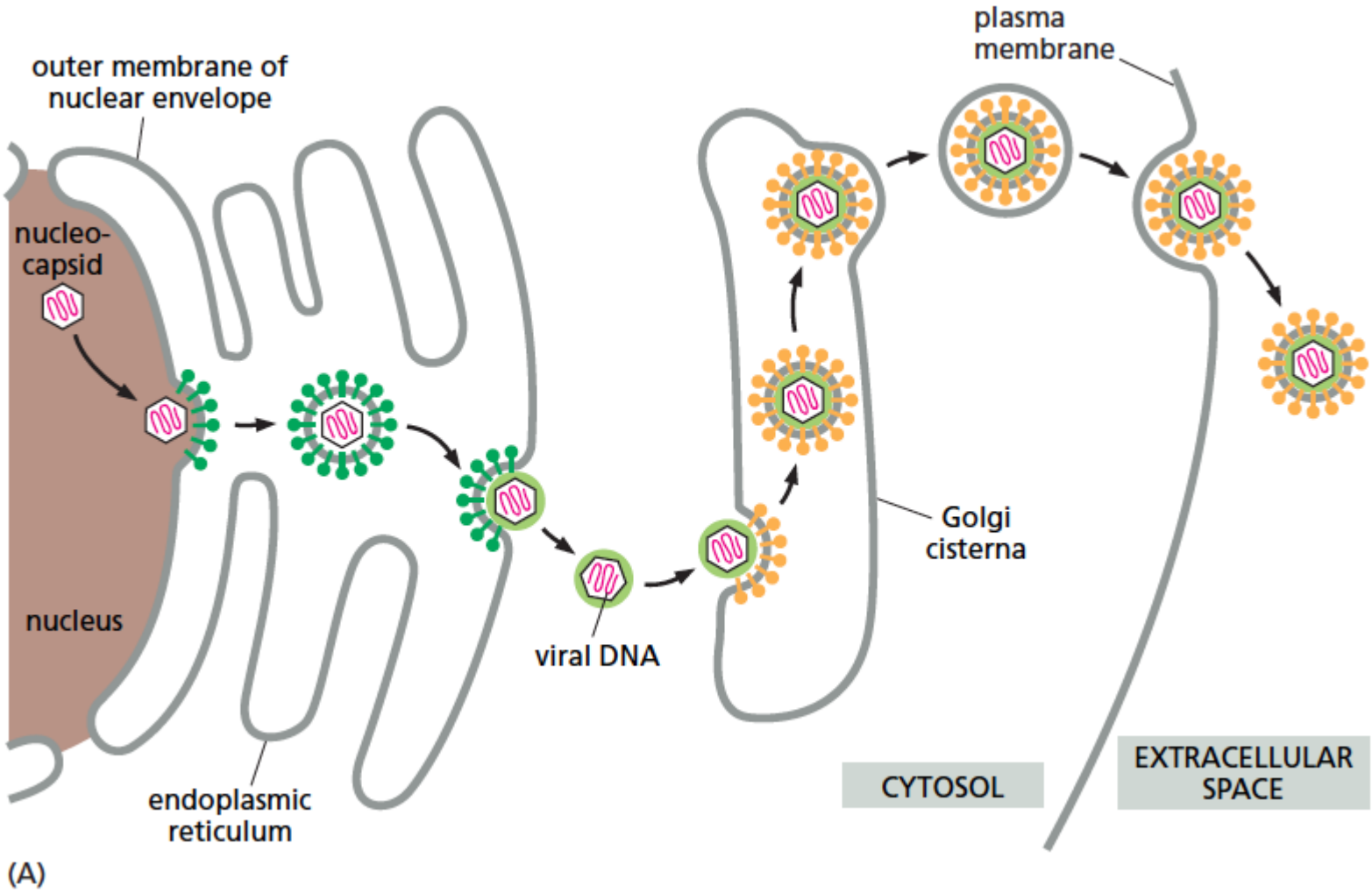
- Different types of viral genomes derive mRNA through various pathways



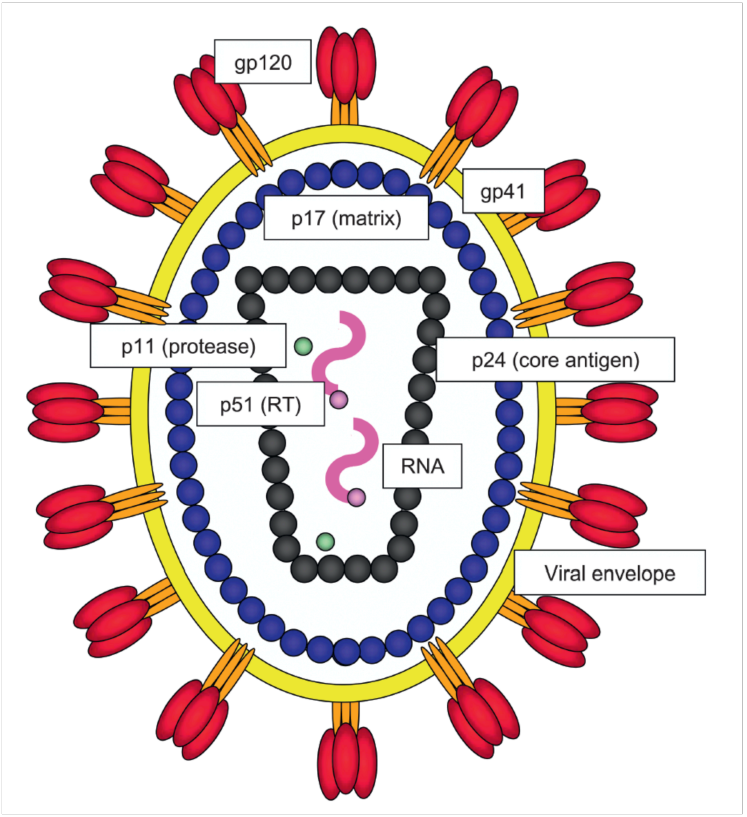
- Viral genomes encode for key proteins essential to viral replication
- Viruses rely completely on host cells for replication machinery including translation of requisite viral proteins
- Different types of nucleic acid genomes utilize varying strategies to arrive at viral mRNA that can then be translated by host cell ribosomes into viral proteins

Mendez, I. I.; Swanson, M. I.; Coombs, K. M. *Clinical Neurovirology Chapter 1: Introduction to Virus Structure, Classification, Replication, and Hosts* **2003**, Mercel Dekker Inc. pp 1-20.

- Assembly of new viruses and their exit from the host cell completes the cycle



HIV: 30 Years of Research and Drug Discovery



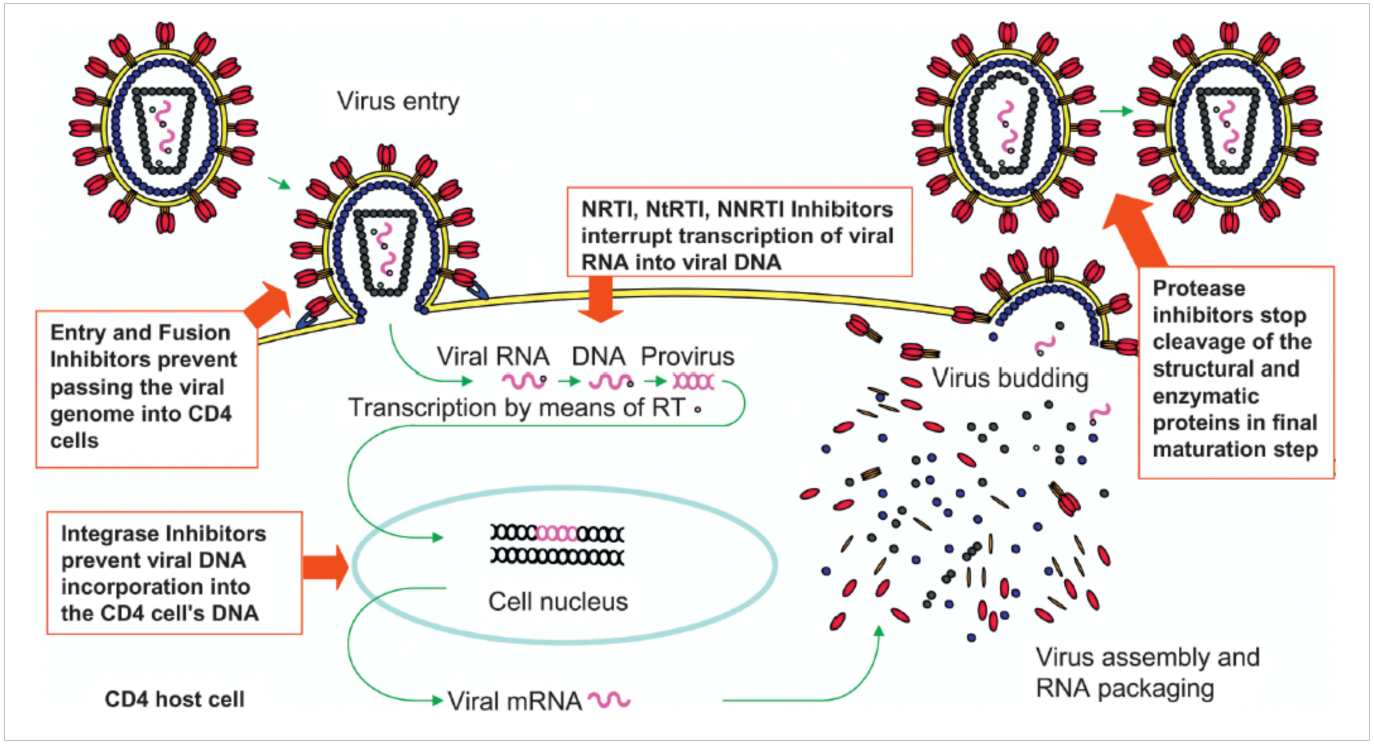
- First cases of HIV were documented in 1983, now accepted that virus developed from simian immunodeficiency virus (SIV)
- Since 1983 more than 60 million people have been infected and more than 25 million have died
- There are currently twenty-five anti-HIV compounds that have been formally approved for clinical treatment

Andrade, C. H.; de Freitas, L. M.; de Oliveira, V. *Brazilian J. Pharm. Sci.* **2011**, *47*, 209

Coman, R. M.; McKenna, R. *RSC Biomol. Sci. 21: Structural Virology*. Chapter 15 pp 293-318.

HIV: 30 Years of Research and Drug Discovery

■ Life cycle of HIV gives rise to four therapeutic targets for pharmaceuticals



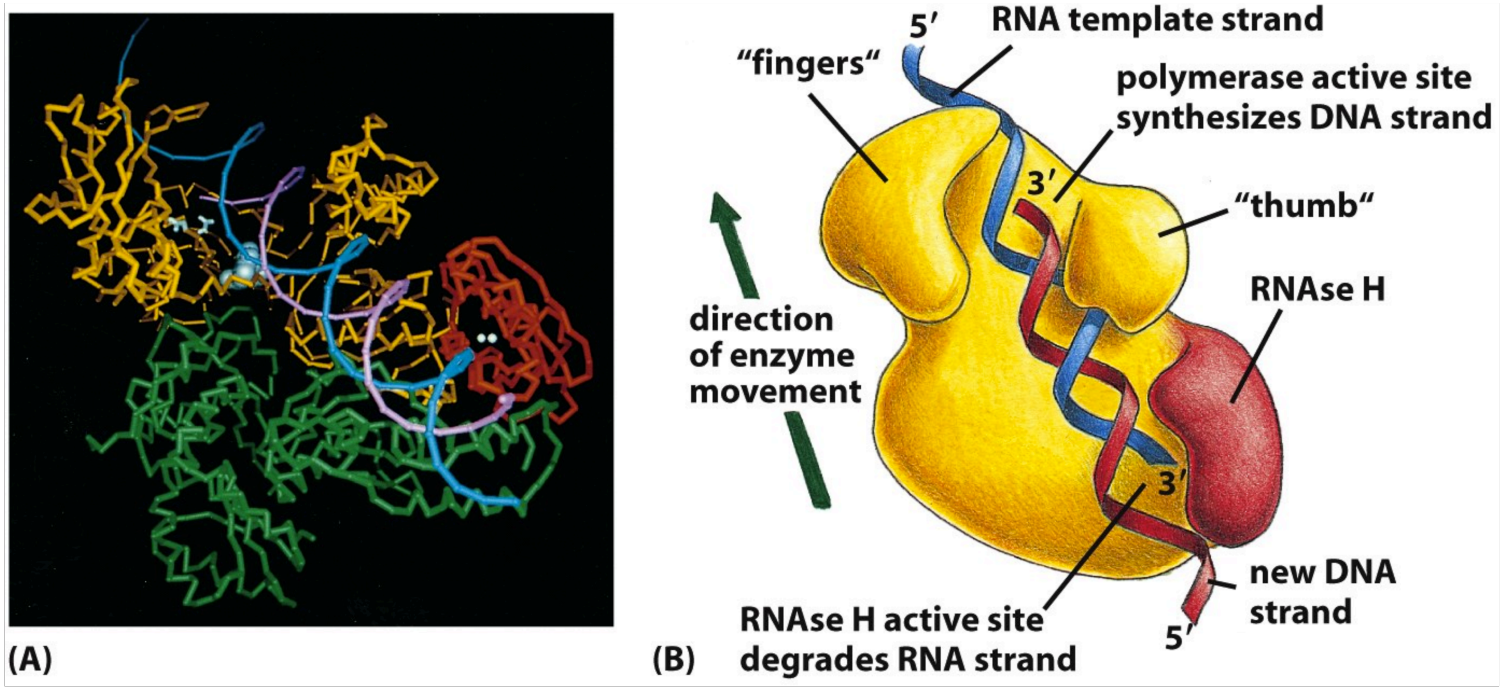
■ Four classes of HIV drugs have been developed: 1. Reverse transcriptase inhibitors 2. Integrase inhibitors 3. Protease inhibitors 4. Fusion and entry inhibitors

Andrade, C. H.; de Freitas, L. M.; de Oliveira, V. *Brazilian J. Pharm. Sci.* **2011**, *47*, 209

Coman, R. M.; McKenna, R. *RSC Biomol. Sci. 21: Structural Virology*. Chapter 15 pp 293-318.

HIV: 30 Years of Research and Drug Discovery

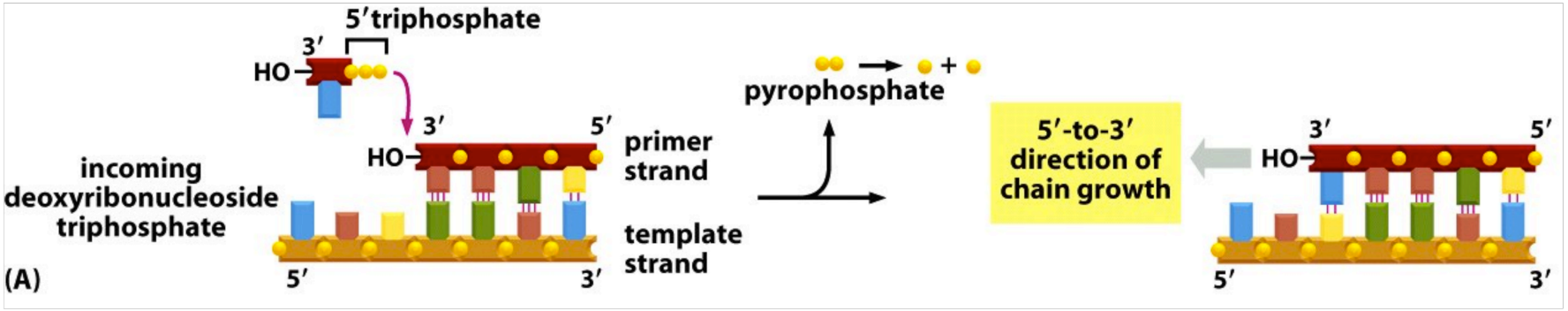
- Many reverse transcriptase drugs are nucleoside mimics (NRTIs)

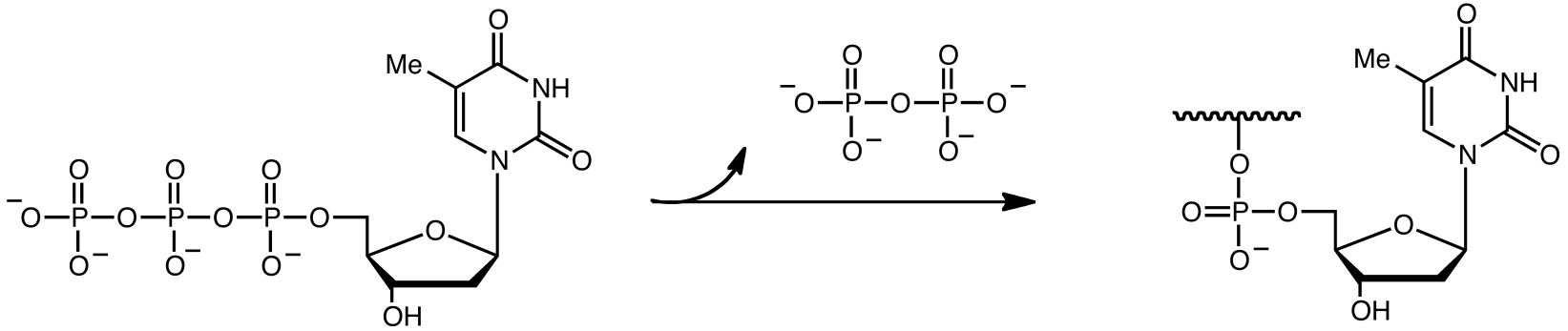


- NRTIs are competitive binders for the active site of reverse transcriptase
- NRTIs lack a 3' hydroxy group and therefore stall polymerization of the DNA strand once incorporated

Molecular Biology of the Cell 5th Ed.; Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

- Many reverse transcriptase drugs are nucleoside mimics (NRTIs)



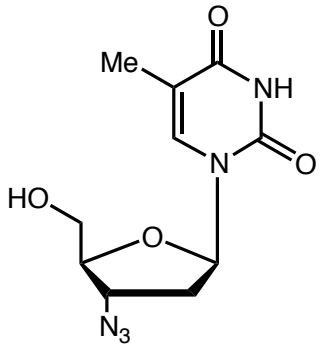


- NRTIs are competitive binders for the active site of reverse transcriptase
- NRTIs lack a 3' hydroxy group and therefore stall polymerization of the DNA strand once incorporated

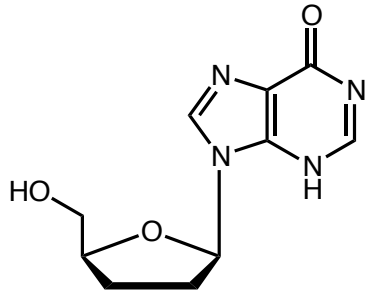
Molecular Biology of the Cell 5th Ed.; Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

HIV: 30 Years of Research and Drug Discovery

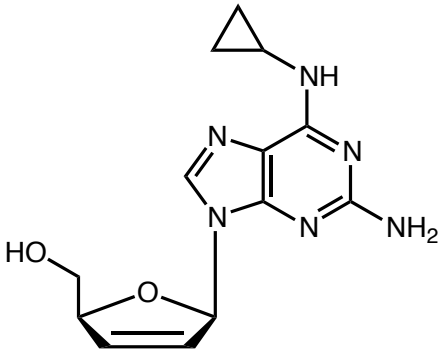
■ Many reverse transcriptase drugs are nucleoside mimics (NRTIs)



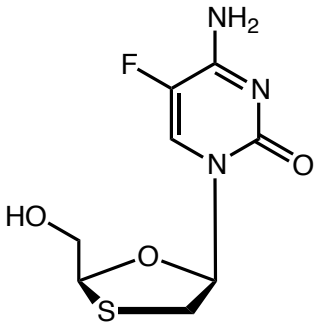
Zidovudine
First HIV drug approved March 20, 1987
Developed by Burroughs-Wellcome (now GSK)



Didanosine
Second HIV drug approved October 9, 1991
Developed by NCI and licensed to BMS



Abacavir
Approved December 18, 1998
Developed by GSK

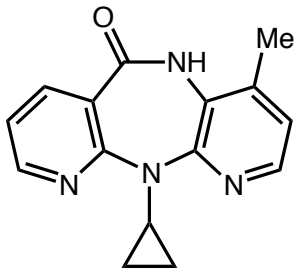


Emtricitabine
Approved July 2, 2003
Developed by Scientists at Emory
Sold to Triangle which was bought by Gilead

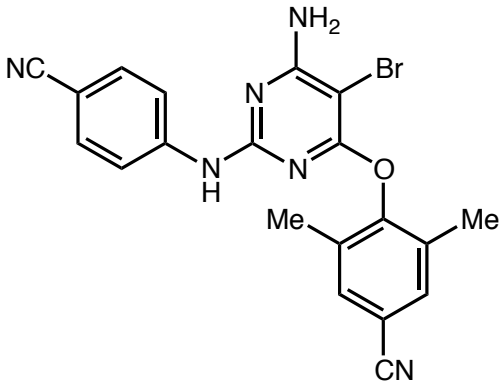
Coman, R. M.; McKenna, R. *RSC Biomol. Sci. 21: Structural Virology*. Chapter 15 pp 293-318.

HIV: 30 Years of Research and Drug Discovery

- Other drugs target allosteric sight of reverse transcriptase



Nevirapine
First NNRTI drug approved June 21, 1996
Developed by Boehringer Ingelheim



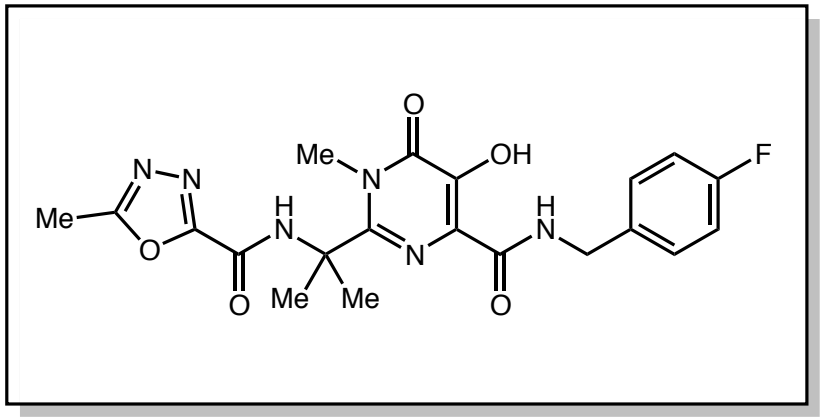
Etravirine
Latest NNRI drug approved January 18, 2008
Developed by Johnson and Johnson

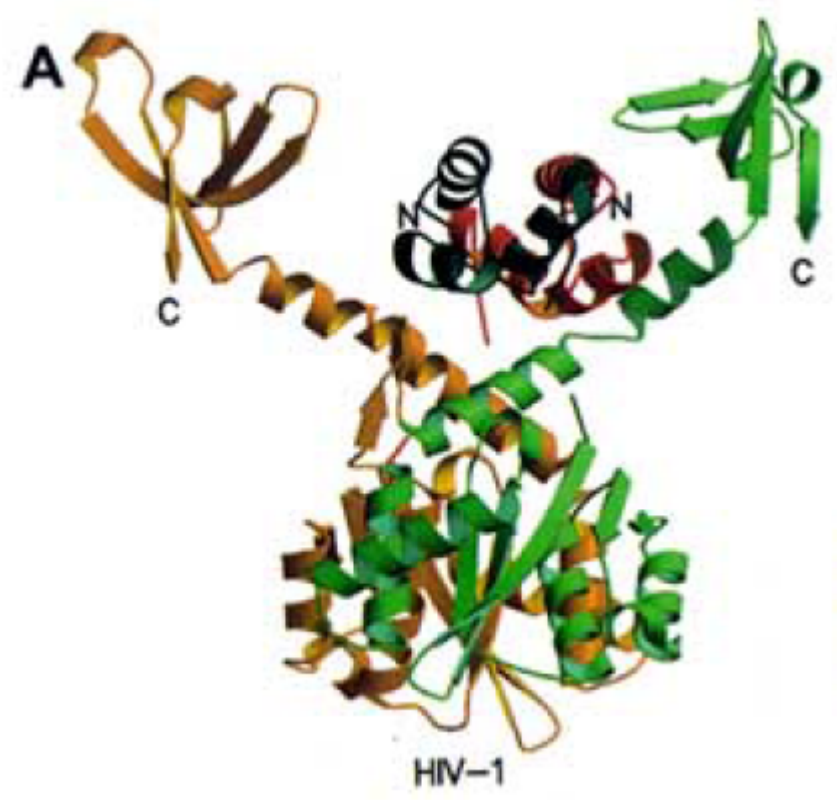
- This class of HIV drug is known as non-nucleoside reverse transcriptase inhibitors (NNRTIs)
- Once bound to the allosteric site normal protein conformational freedom is restricted causing inactivation

Coman, R. M.; McKenna, R. *RSC Biomol. Sci. 21: Structural Virology*. Chapter 15 pp 293-318.

HIV: 30 Years of Research and Drug Discovery

- One drug approved for inhibition of HIV integrase protein

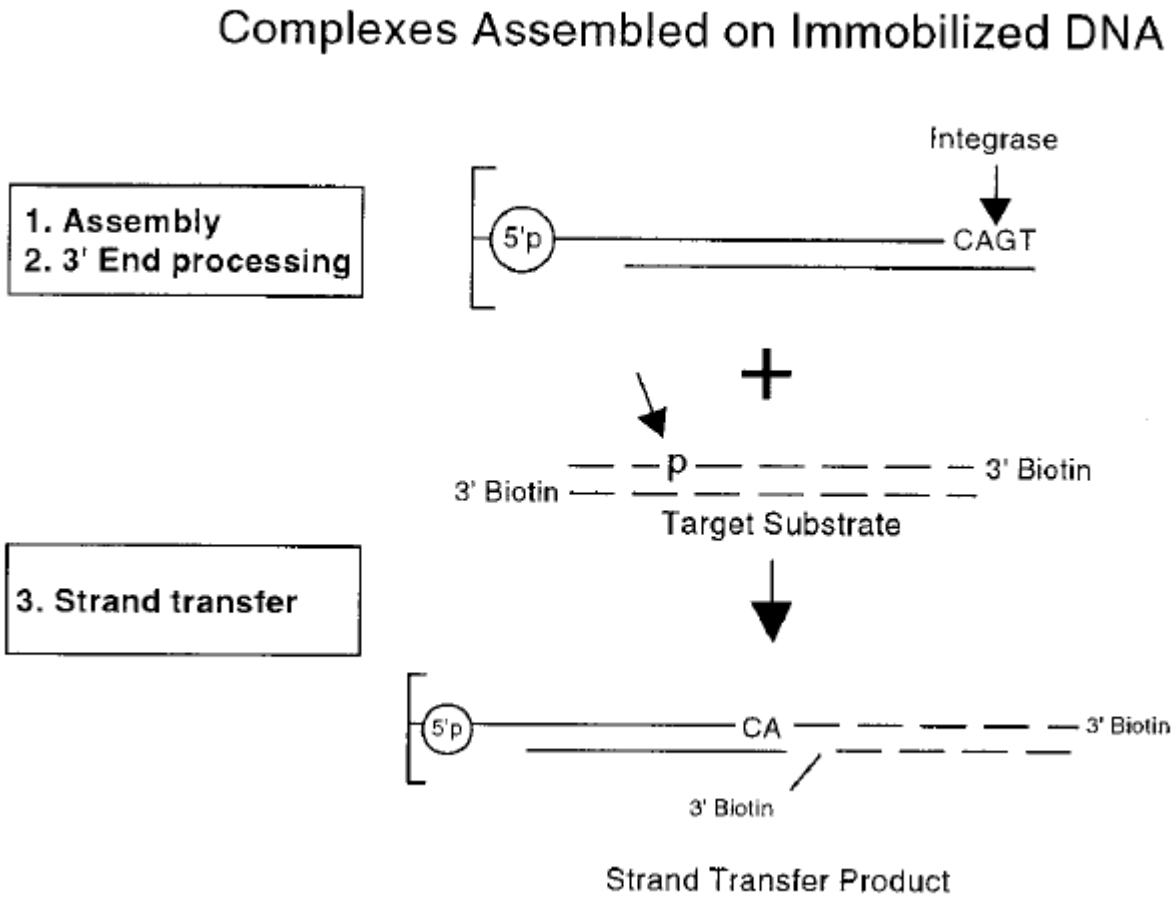




- A preformed integrase complex is needed to initiate the strand transfer step of DNA integration
- Raltegravir, developed by Merck and approved on October 12, 2007, binds to this complex and dissociates at a rate slower than the half-life of the preintegration complex essentially rendering it an irreversible binder

Chiu, T. K.; Davies, D. R. *Curr. Top. Med. Chem.* **2004**, *4*, 965.
Coman, R. M.; McKenna, R. *RSC Biomol. Sci. 21: Structural Virology*. Chapter 15 pp 293-318.

- One drug approved for inhibition of HIV integrase protein

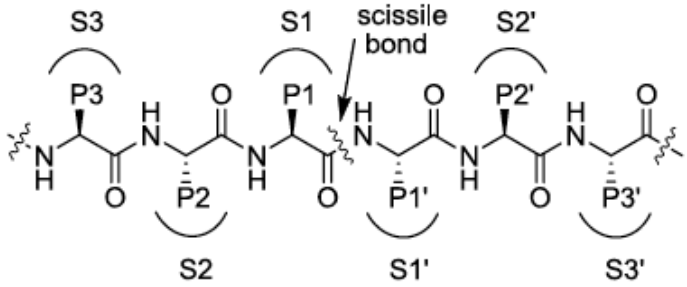


- A preformed integrase complex is needed to initiate the strand transfer step of DNA integration
- Raltegravir, developed by Merck and approved on October 12, 2007, binds to this complex and dissociates at a rate slower than the half-life of the preintegration complex essentially rendering it an irreversible binder

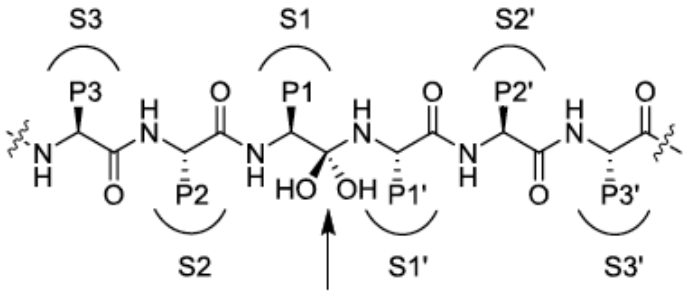
Hazuda, D. J. *et. al. Science* **2000**, *287*, 646.
Coman, R. M.; McKenna, R. *RSC Biomol. Sci. 21: Structural Virology*. Chapter 15 pp 293-318.

HIV: 30 Years of Research and Drug Discovery

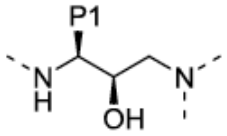
- Protease inhibitors act by mimicking transition state of amide bond hydrolysis



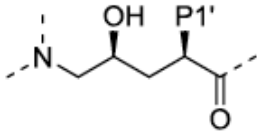
Polyprotein substrate



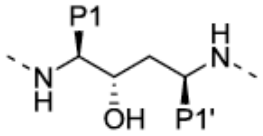
Transition state intermediate



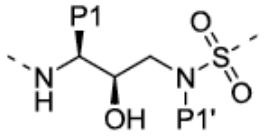
Hydroxyethylamine **I**



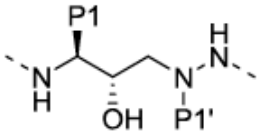
Hydroxyaminopentane **II**



Hydroxyethylene **III**



Hydroxyethylamino-sulfonamide **IV**



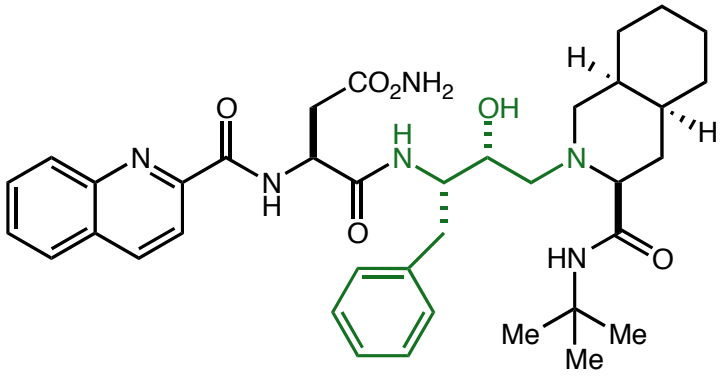
Aza-hydroxyethylamine **V**

- By blocking protease function virus particles remain unable to infect host cells as key enzymes and proteins needed for cell entry and genome replication remain inactive in their pro-enzyme form

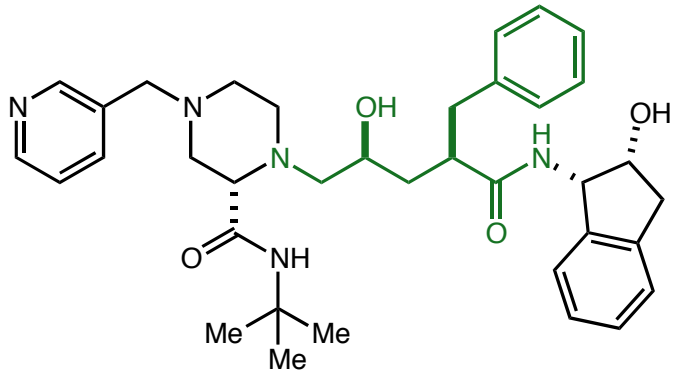
Schiffer, C. A. *Viruses* **2010**, *2*, 2510.

HIV: 30 Years of Research and Drug Discovery

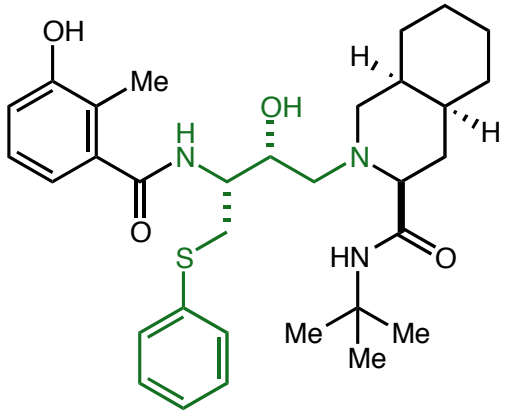
■ Nine drugs FDA approved for targeting HIV protease enzyme



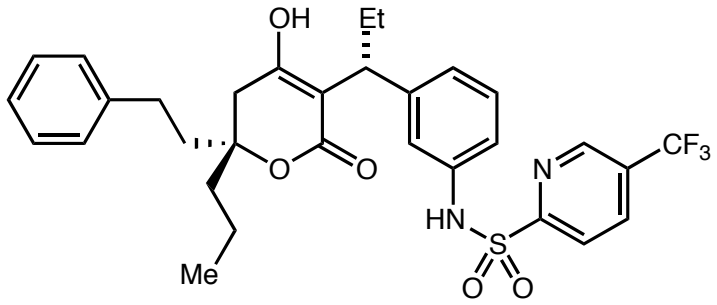
Saquinavir
First protease drug approved 1995
Developed by Roche



Indinavir
Second protease drug approved 1996
Developed by Merck



Nelfinavir
Protease drug approved 1997
Developed by Agouron

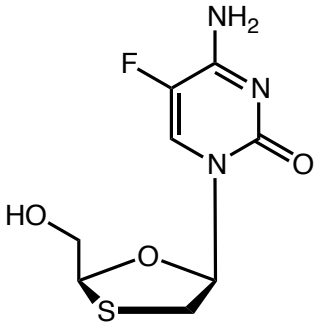


Tipranavir
Only non-peptidic protease drug approved 2005
Developed by BI

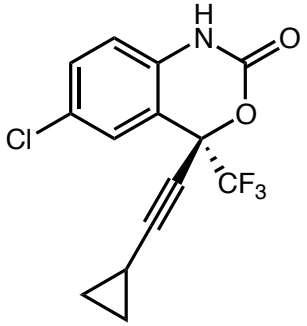
Schiffer, C. A. *Viruses* **2010**, *2*, 2510.

HIV: 30 Years of Research and Drug Discovery

- Rate of mutation found in HIV virus requires drug cocktails for effective treatment

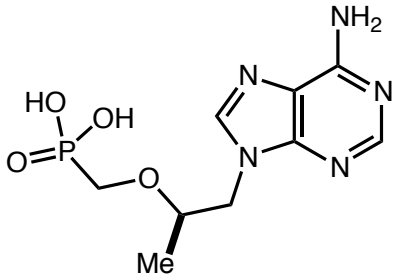


Emtricitabine
Gilead



Efavirenz
BMS

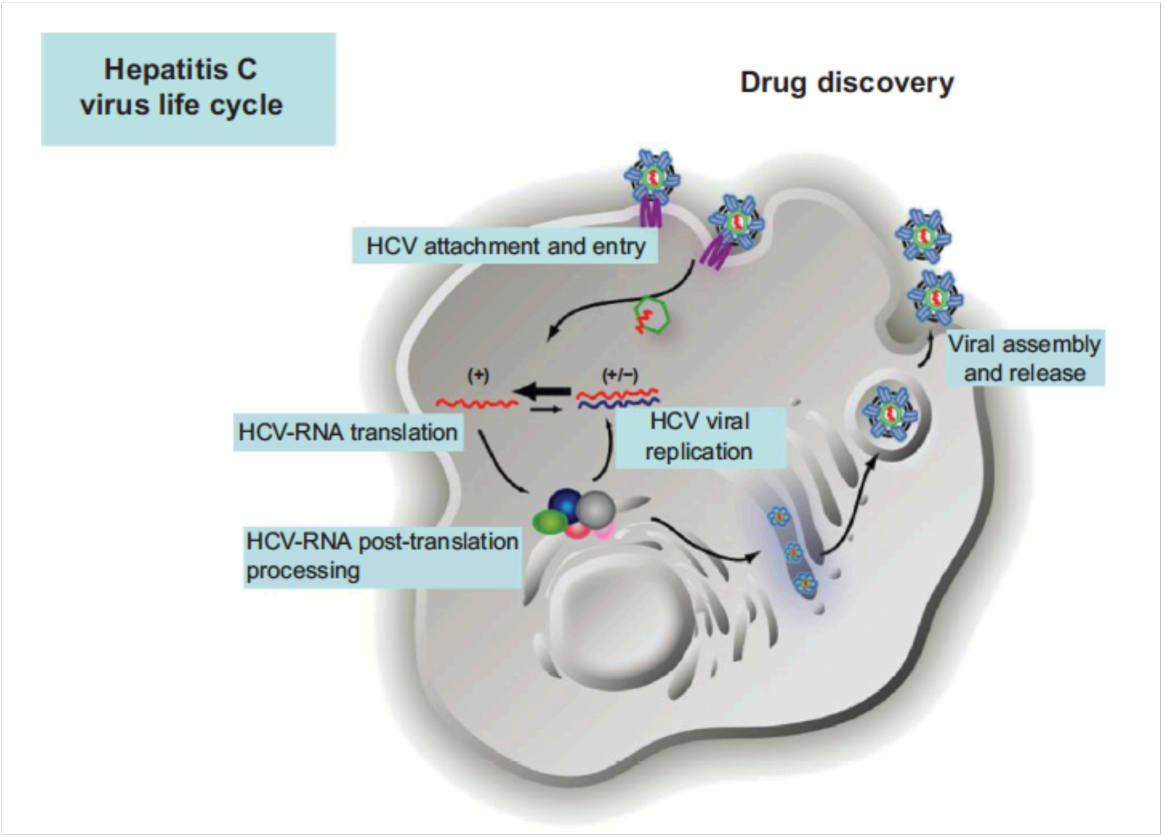
Tenofovir
Gilead



- Rate of high mutation is primarily caused by reverse transcriptase's inability to proof read and correct errors
- Genetic recombination also occurs due to reverse transcriptase's ability to switch between either copy of HIV's ssRNA genome creating recombinant genomes in progeny

Hepatitis C Virus: A Leading Cause of Liver Disease

- HCV is a positive sense ssRNA virus that infects human liver cells

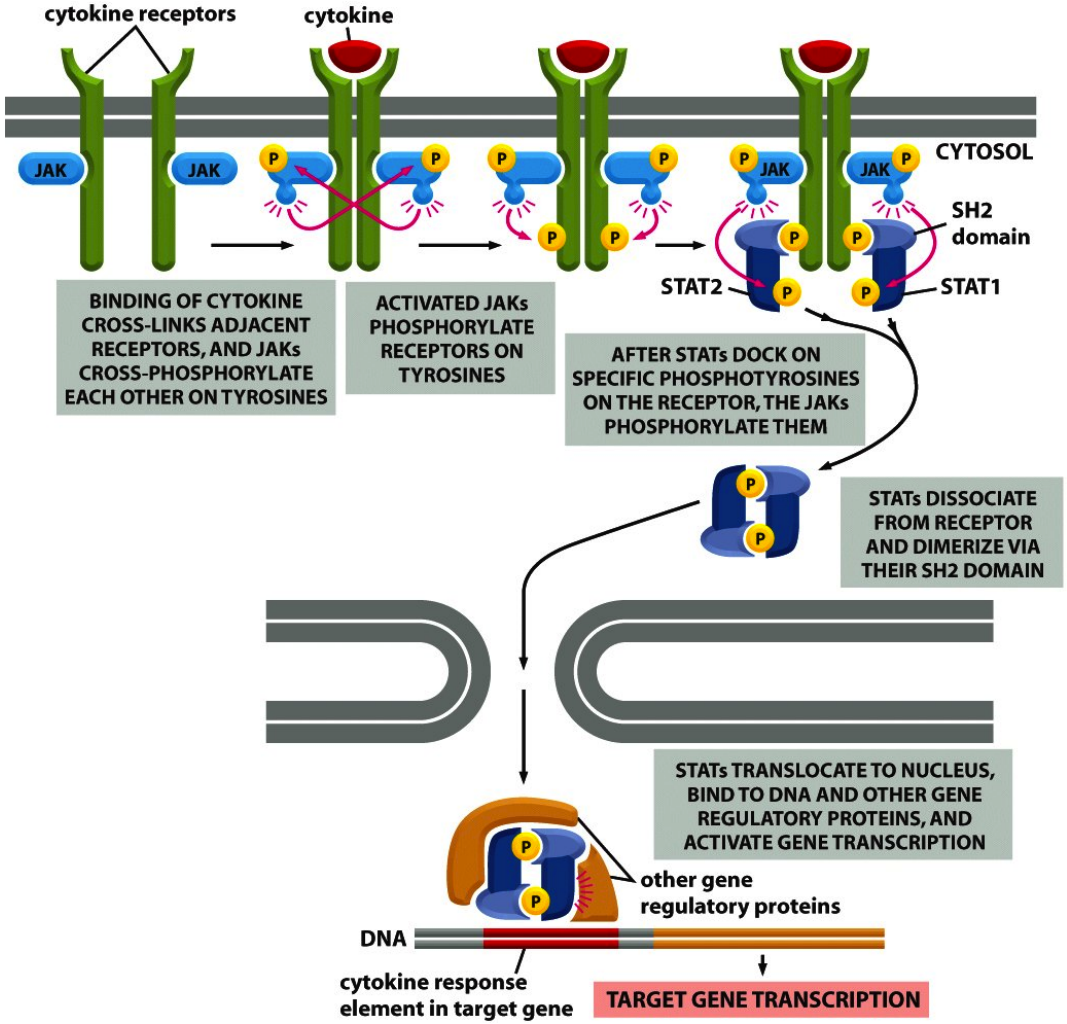


- An estimated 200 million people are infected with HCV world-wide (five times more than HIV)
- HCV is responsible for over 50% of the liver transplants performed due to chronic liver disease
- In contrast to HIV, HCV does not incorporate its genome into host cell enabling a therapeutic goal of clearing the virus completely from the infected individual. This happens innately in 20% of infected individuals

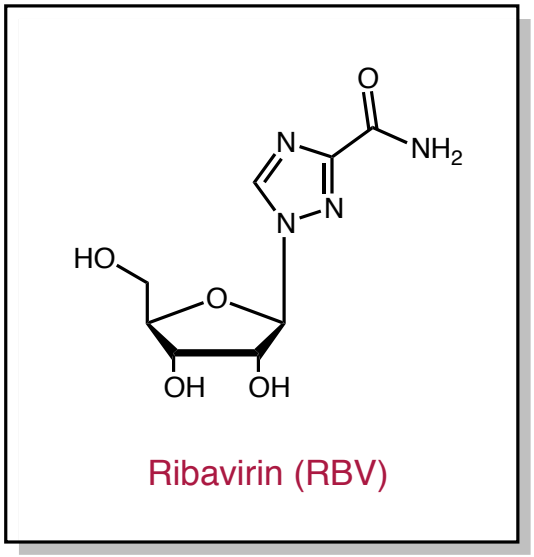
Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Hepatitis C Virus: A Leading Cause of Liver Disease

- HCV current standard of care relies on activating innate immune system



- Current standard of care for HCV involves injections of polyethylene glycol (PEG) modified interferon-α. INF-α is a natural signaling protein (cytokine) that is triggered by cells in response to viral infection.
- INF-α initiates a signal-transduction cascade that upregulates over 300 gene products responsible for immune system activation



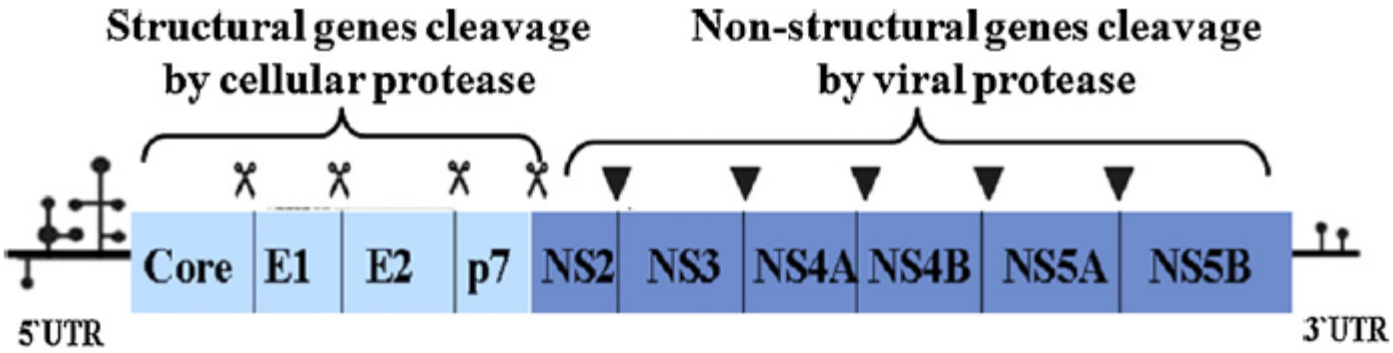
Ribavirin (RBV)

Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Molecular Biology of the Cell 5th Ed.; Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

Hepatitis C Virus: A Leading Cause of Liver Disease

- Genomic HCV ssRNA is transcribed directly into 3010 amino acid polyprotein



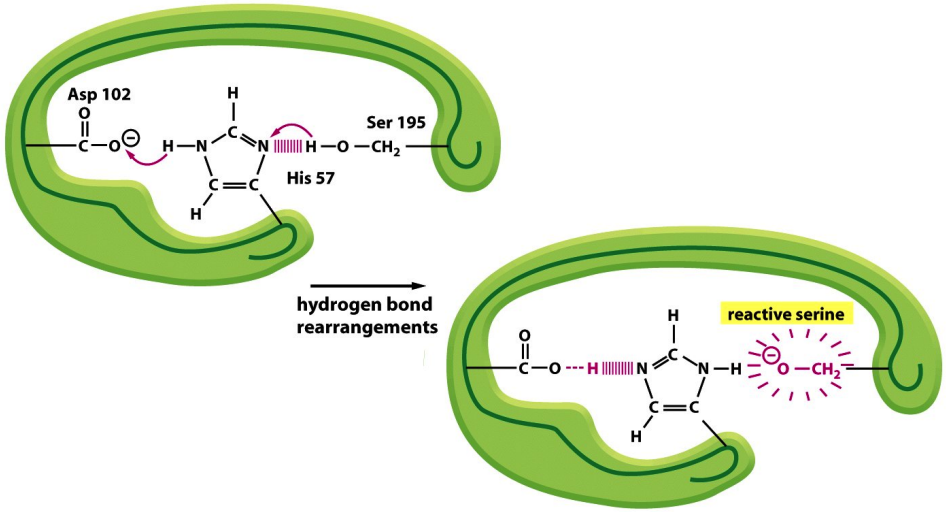


Figure 3-38 Molecular Biology of the Cell 5/e (© Garland Science 2008)

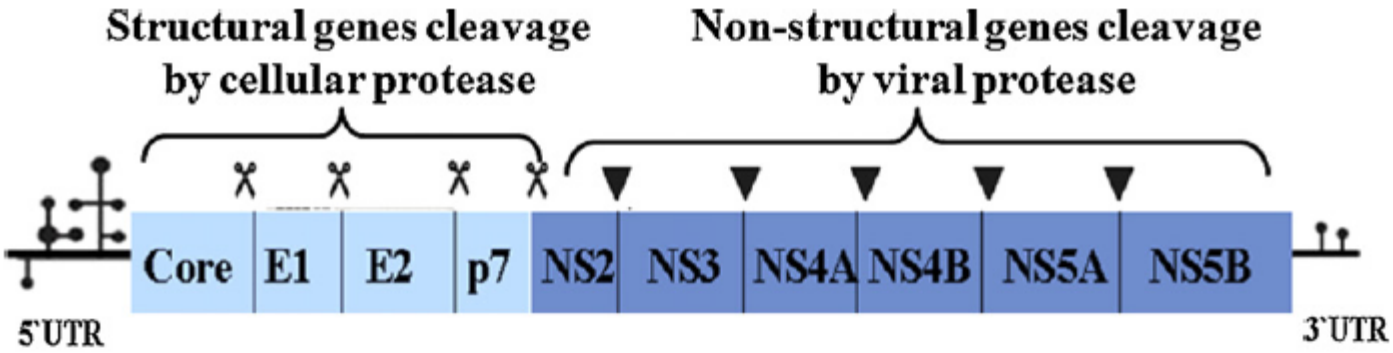
- One domain of NS3 and a heterodimer between NS3 and NS4A are serine proteases responsible for the cleavage of polyprotein
- NS3 also has an RNA helicase function

Khaliq, S.; Jahan, S.; Pervaiz, A. *Infection, Genetics, and Evolution* **2011**, *11*, 543.

Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Hepatitis C Virus: A Leading Cause of Liver Disease

- Genomic HCV ssRNA is transcribed directly into 3010 amino acid polyprotein



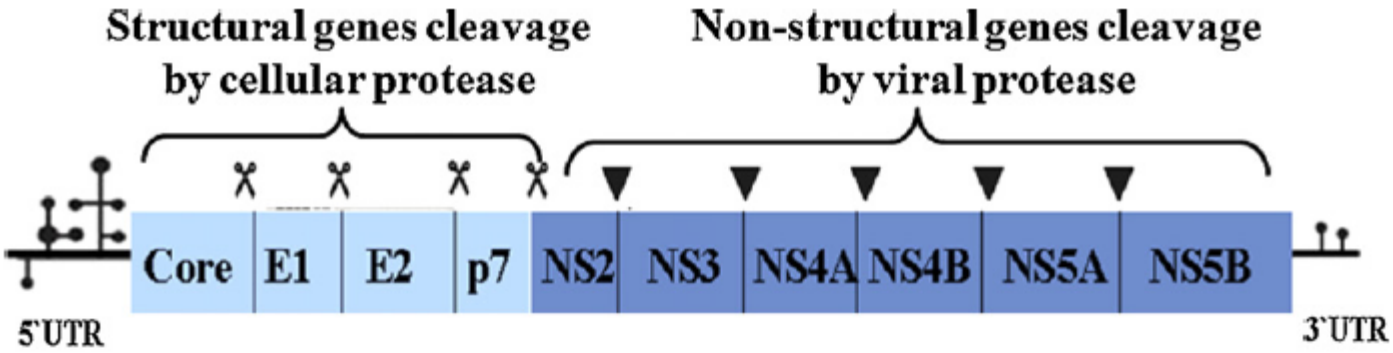
- One domain of NS3 and a heterodimer between NS3 and NS4A are serine proteases responsible for the cleavage of polyprotein
- NS3 also has an RNA helicase function

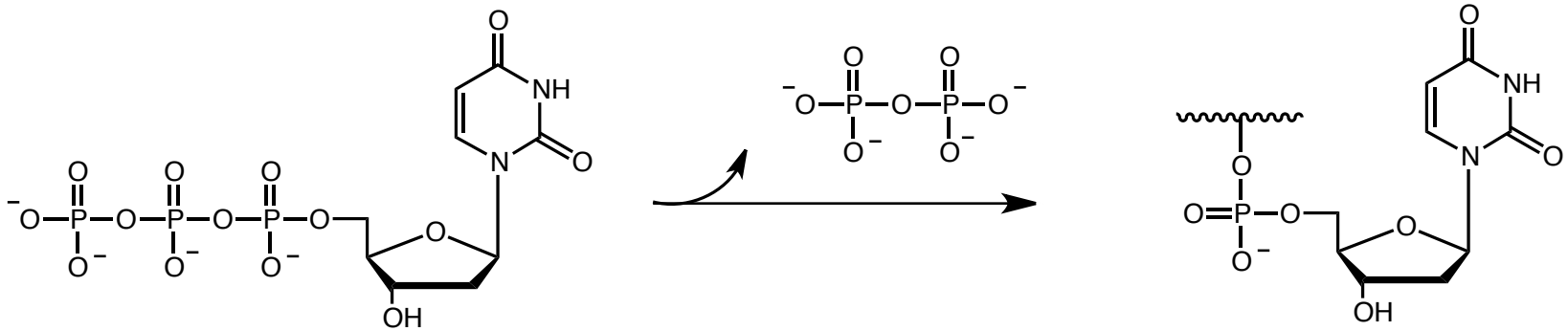
Khaliq, S.; Jahan, S.; Pervaiz, A. *Infection, Genetics, and Evolution* **2011**, *11*, 543.

Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Hepatitis C Virus: A Leading Cause of Liver Disease

- Genomic HCV ssRNA is transcribed directly into 3010 amino acid polyprotein





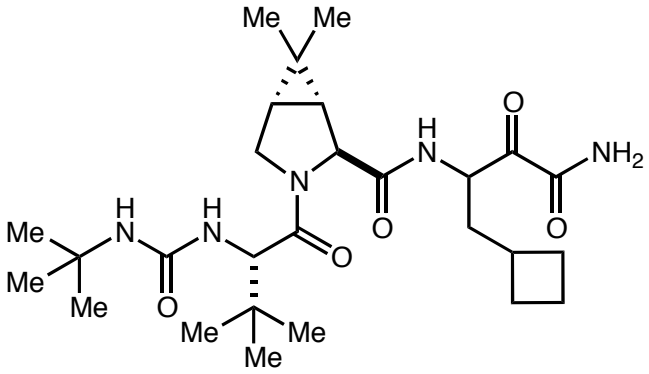
- NS5B is a RNA-dependent RNA polymerase (RdRp) which is responsible for replicating RNA genome
- RdRp's are specific to RNA viruses without a DNA phase and, like reverse transcriptases, are unable to proof read and have a relatively high error rate (about one error per RNA strand copied for HCV)

Khaliq, S.; Jahan, S.; Pervaiz, A. *Infection, Genetics, and Evolution* **2011**, *11*, 543.

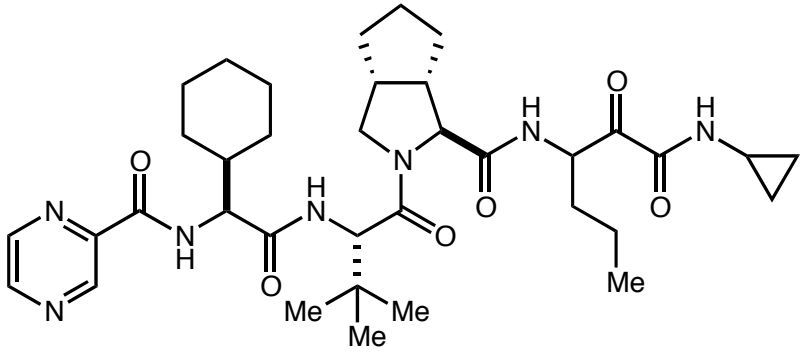
Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Hepatitis C Virus: A Leading Cause of Liver Disease

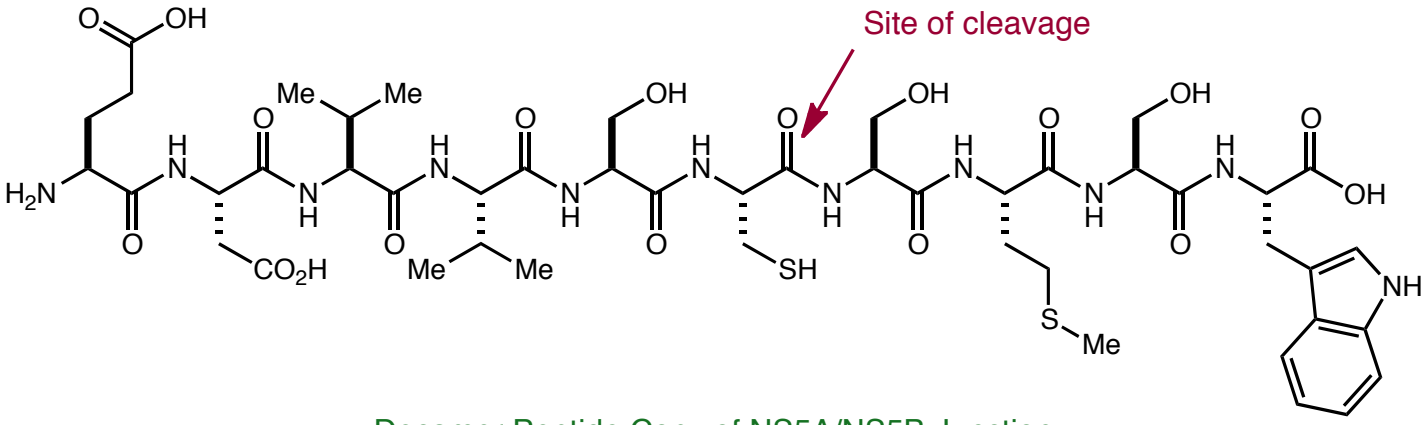
■ Two drugs that inhibit the NS3/4A serine protease were approved in 2011



Boceprevir
May 13, 2011
Developed by Schering-Plough (acquired by Merck)



Telaprevir
April 28, 2011
Developed by Vertex

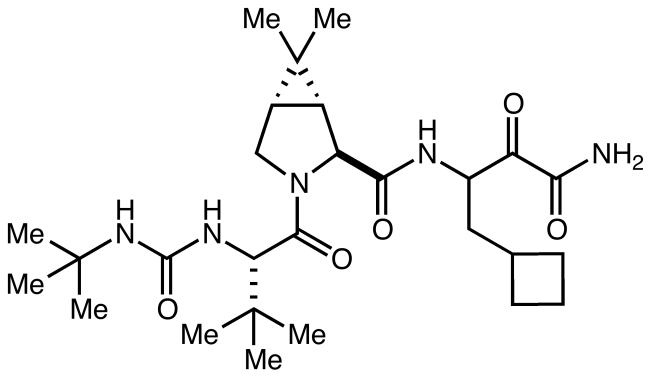


Decamer Peptide Copy of NS5A/NS5B Junction

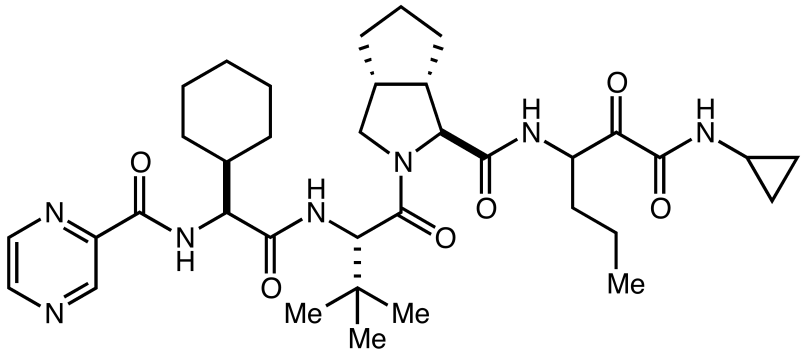
Kwong, A. D.; Kauffman, R. S.; Hurter, P.; Mueller, P. *Nature Biotechnology* **2011**, *29*, 993.
Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Hepatitis C Virus: A Leading Cause of Liver Disease

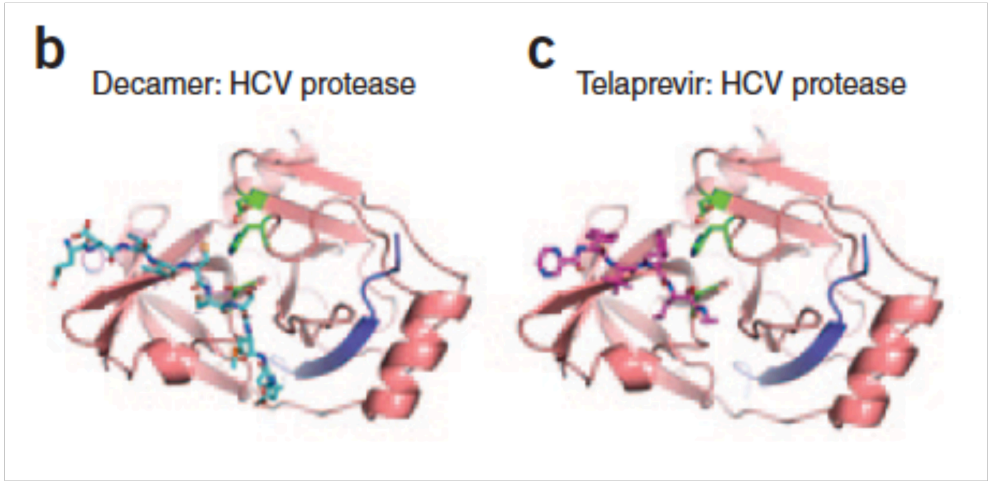
- Two drugs that inhibit the NS3/4A serine protease were approved in 2011



Boceprevir
May 13, 2011
Developed by Schering-Plough (acquired by Merck)



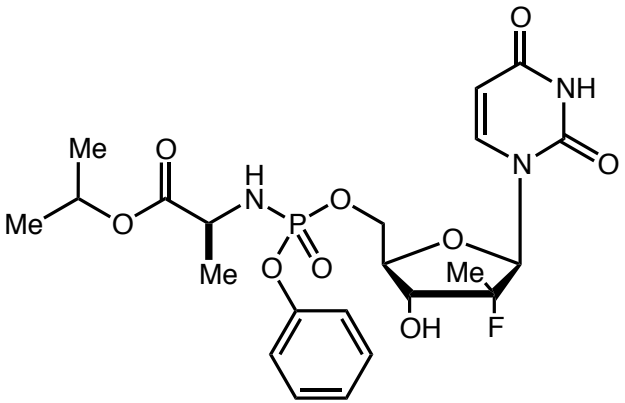
Telaprevir
April 28, 2011
Developed by Vertex



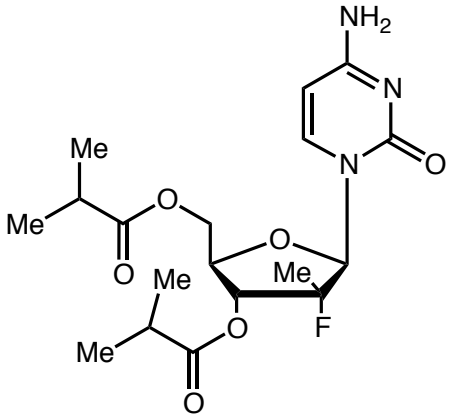
Kwong, A. D.; Kauffman, R. S.; Hurter, P.; Mueller, P. *Nature Biotechnology* **2011**, *29*, 993.
Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Hepatitis C Virus: A Leading Cause of Liver Disease

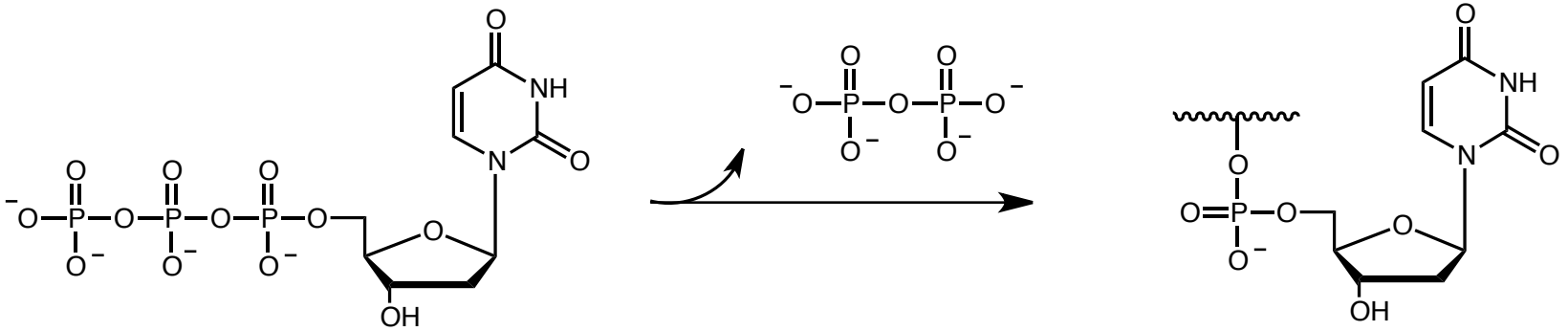
■ Four drugs are currently in phase II trials that are nucleoside mimics that inhibit NS5B the HCV RdRp



PSI-7977
Phase II
Developed by Pharmasset (bought by Gilead)



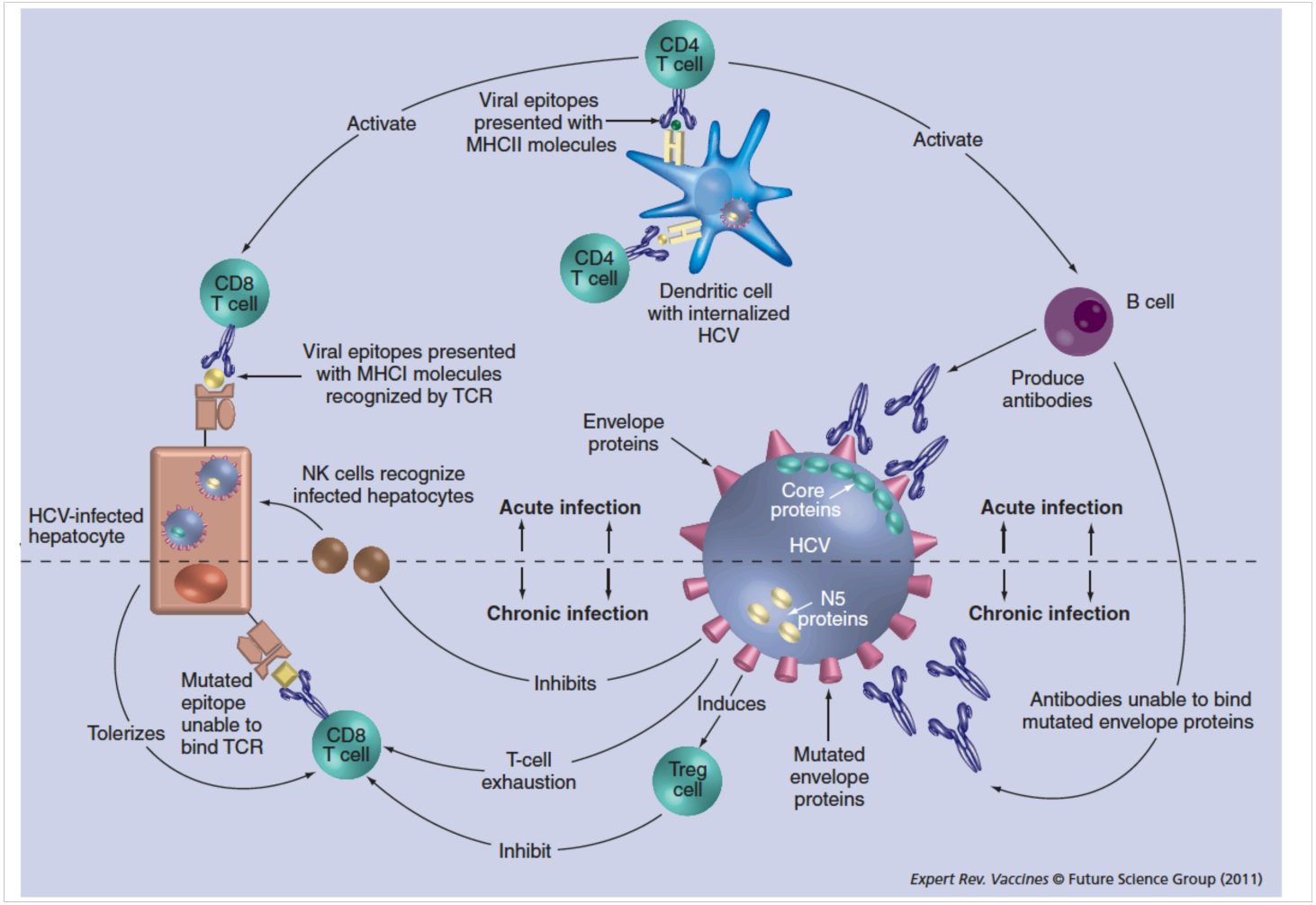
RG-7128
Phase II
Developed by Roche



Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Hepatitis C Virus: A Leading Cause of Liver Disease

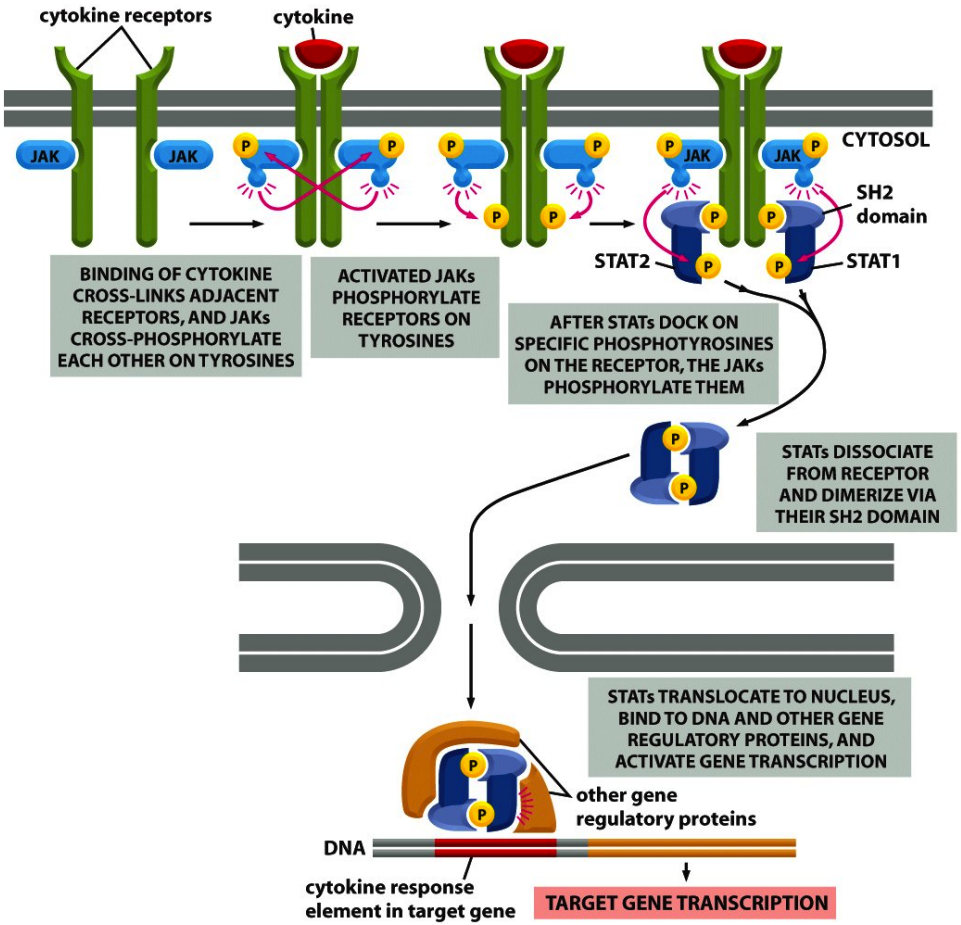
- HCV vaccine development is seen as hopeful based on 20% of patients able to clear the virus

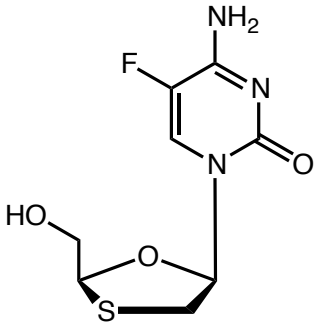


Halliday, J.; Klenerman, P.; Barnes, E. *Expert Rev. Vaccines* **2011**, *10*, 659.

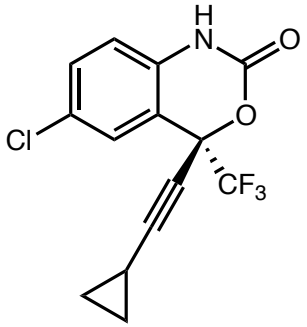
Is There a Third Option for Combating Viral Infections?

- Are there more efficient and general ways to target viruses?



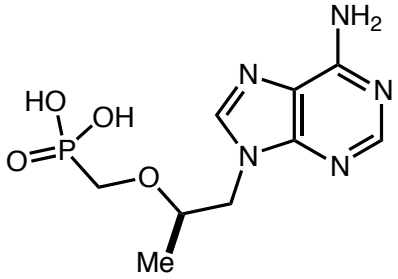


Emtricitabine
Gilead



Efavirenz
BMS

Tenofovir
Gilead

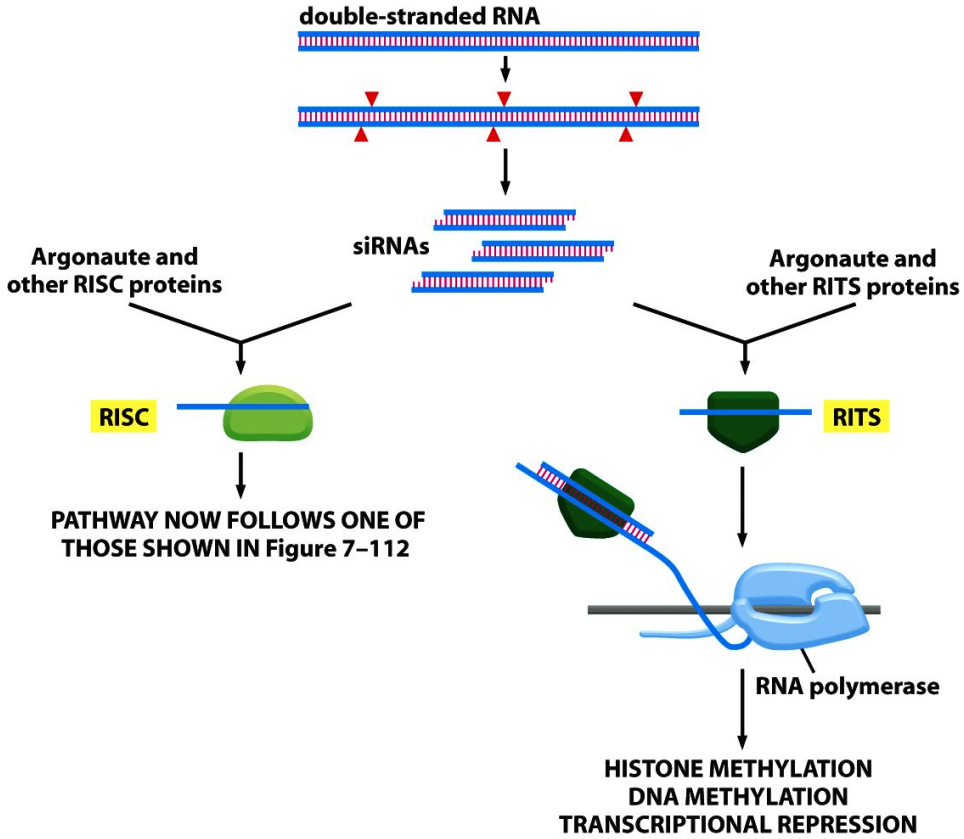


Quer, J.; Buti, M.; Cubero, M.; Guardia, J.; Esteban, R.; Esteban, J. I. *Infect. Drug Resist.* **2010**, *3*, 133.

Molecular Biology of the Cell 5th Ed.; Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

DRACO: A New Approach to Antiviral Therapeutics

- DRACO seeks to act on key biomolecule found in viruses that is not found in vertebrates, dsRNA



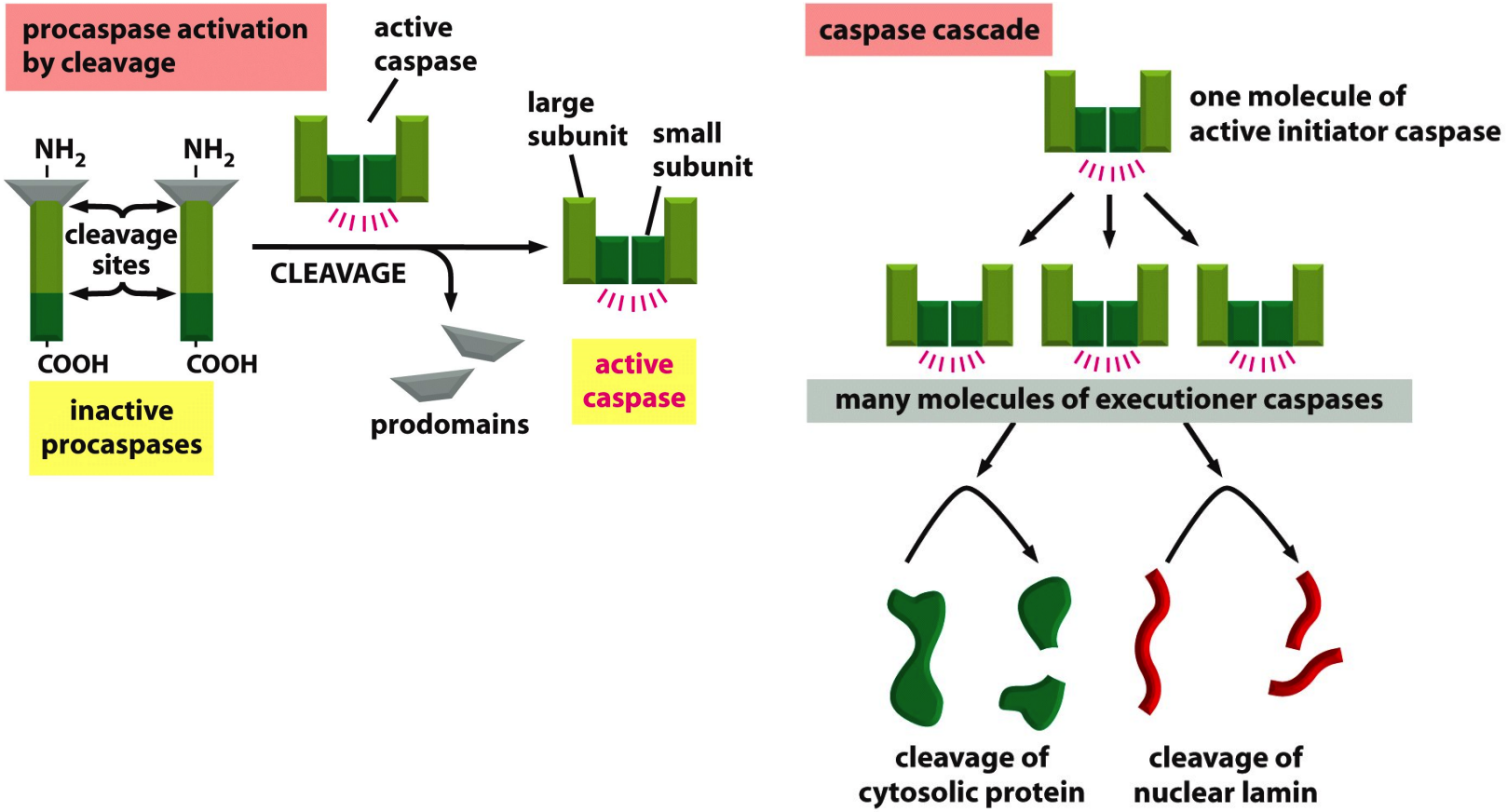
- DRACO stands for double-stranded RNA activated caspase oligomerizer
- Human's have developed antiviral function based on viruses possessing dsRNA. The mechanism for this antiviral function is the basis for RNAi that has been exploited recently in microbiology

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

*Molecular Biology of the Cell 5th Ed.***;** Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

DRACO: A New Approach to Antiviral Therapeutics

- DRACO seeks to act on key biomolecule found in viruses that is not found in vertebrates, dsRNA



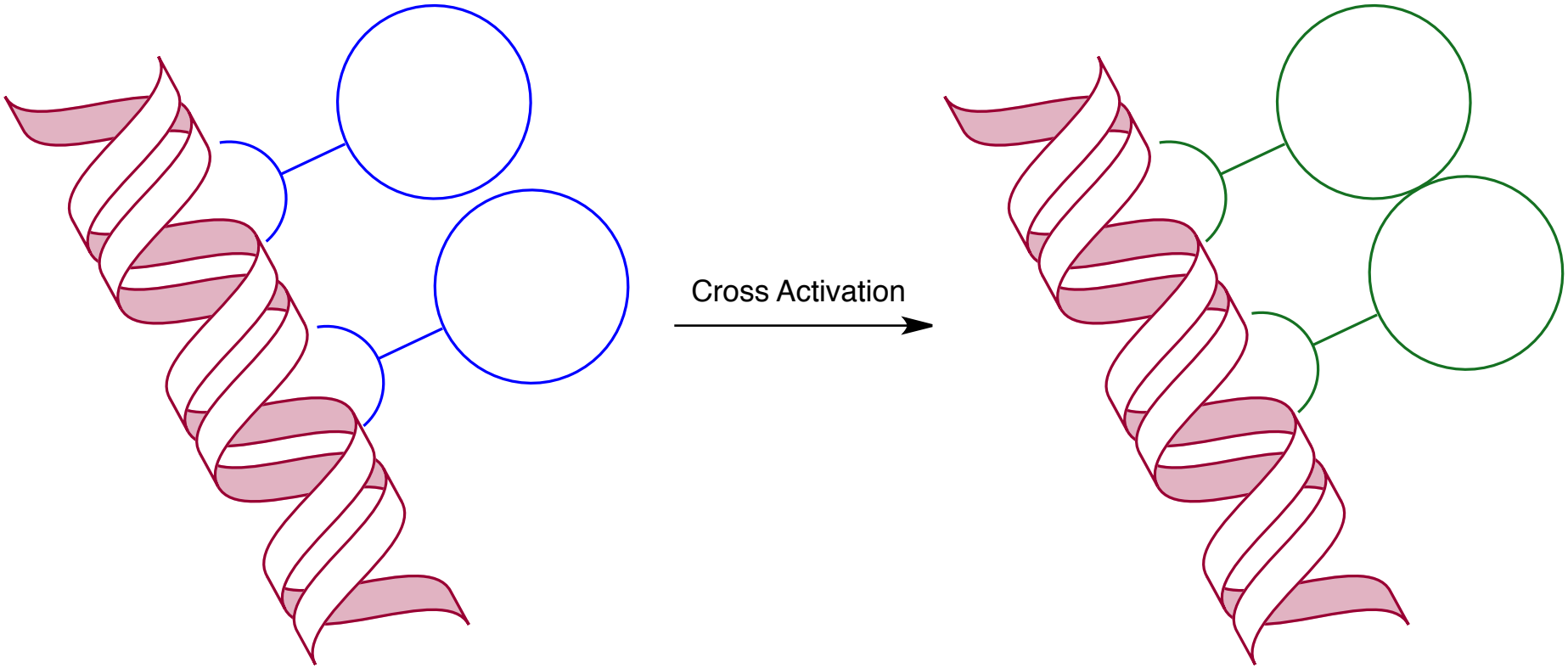
- DRACO works by fusing a dsRNA recognition domain with a protein domain that forms active apoptotic caspases
- By combining recognition of the unique viral biomolecule with an initiator of apoptosis cells that are infected with a virus should selectively kill themselves while healthy cells remain unaffected

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

*Molecular Biology of the Cell 5th Ed.***;** Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

DRACO: A New Approach to Antiviral Therapeutics

- DRACO becomes active when two molecules bind a single RNA and cause cross cleavage

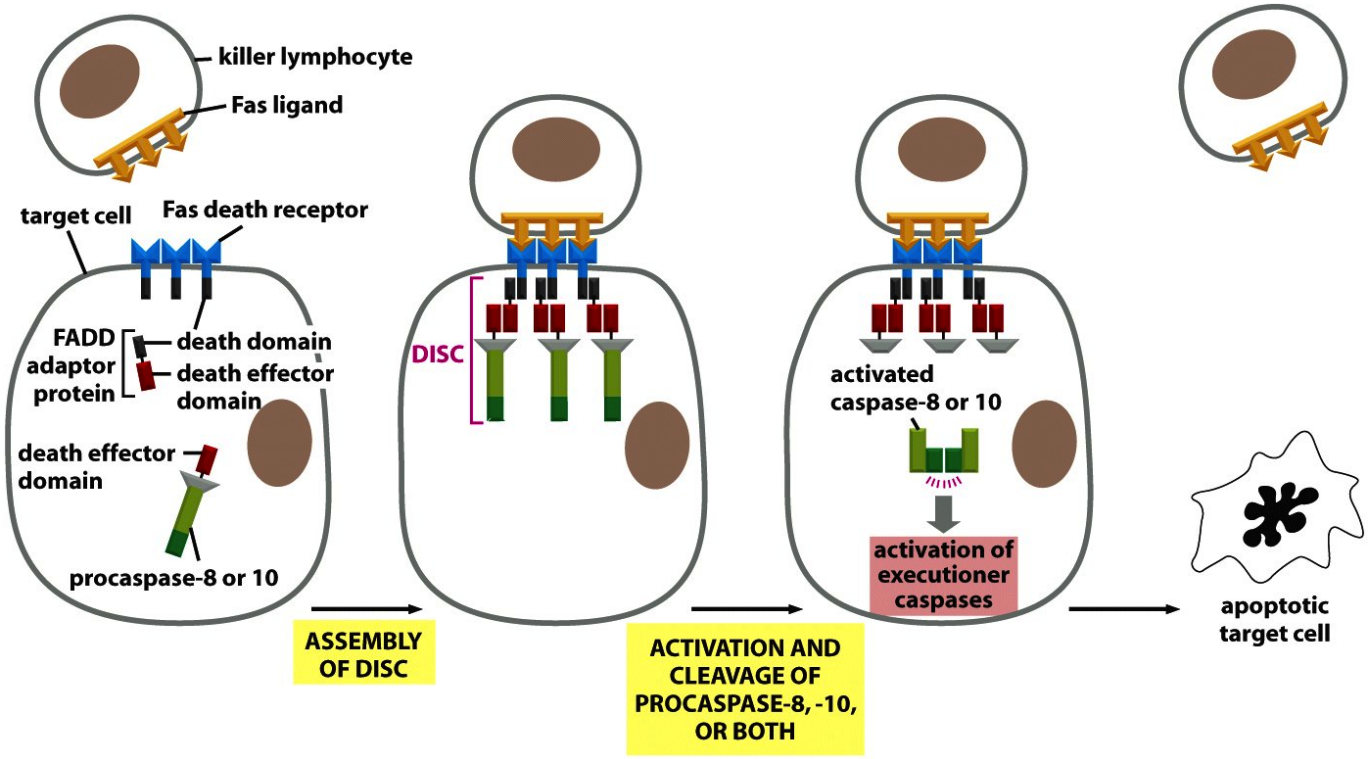


Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

*Molecular Biology of the Cell 5th Ed.***;** Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

DRACO: A New Approach to Antiviral Therapeutics

- DRACO seeks to act on key biomolecule found in viruses that is not found in vertebrates, dsRNA



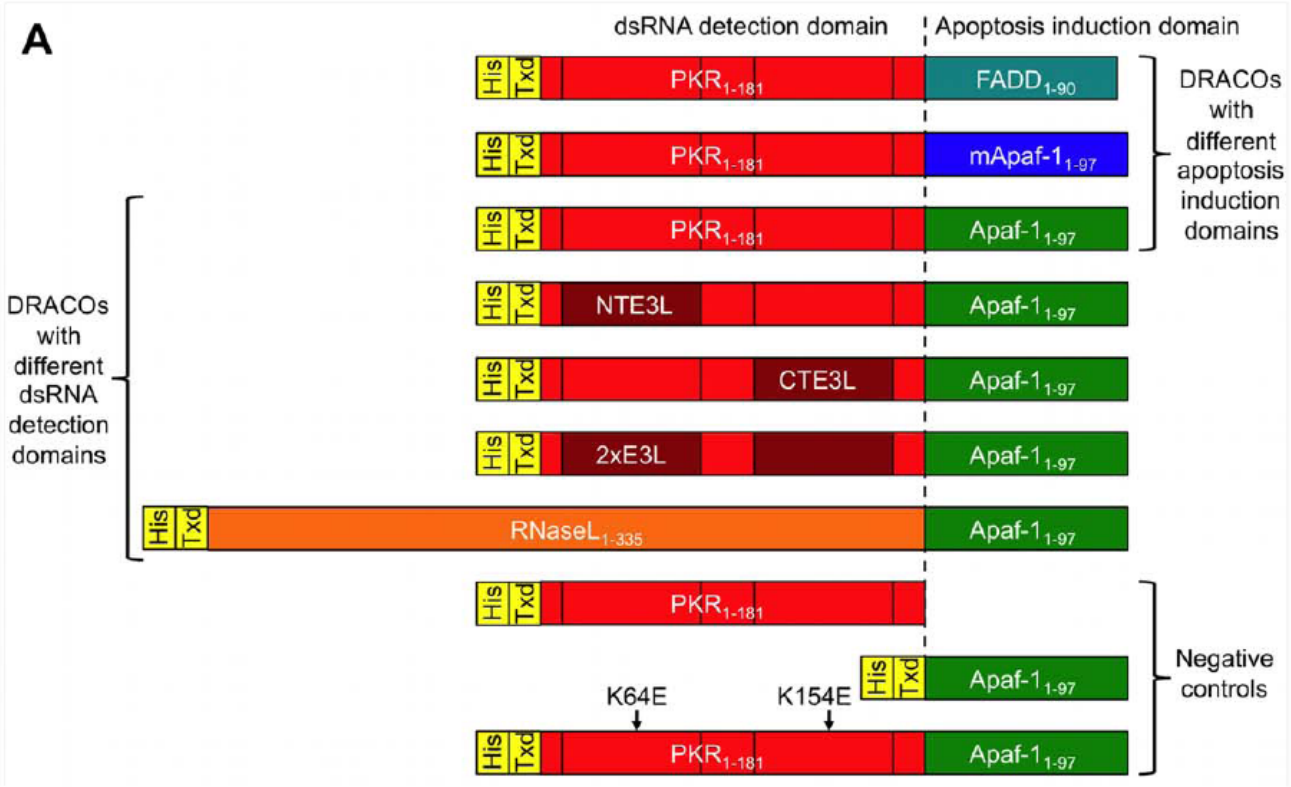
- Viruses have developed defense mechanisms against apoptotic destruction of host cells
- Viral defenses, however, usually act on signaling pathways far upstream from the formation of active caspases

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

Molecular Biology of the Cell 5th Ed.; Alberts, B.; Johnson, A; Lewis, J.; Raff, M.; Roberts, K.; Walter, P.; Garland Science: New York, 2008, pp 1485-1538.

DRACO: A New Approach to Antiviral Therapeutics

- DRACO proteins constructed from linked RNA binding with procaspases binding domains

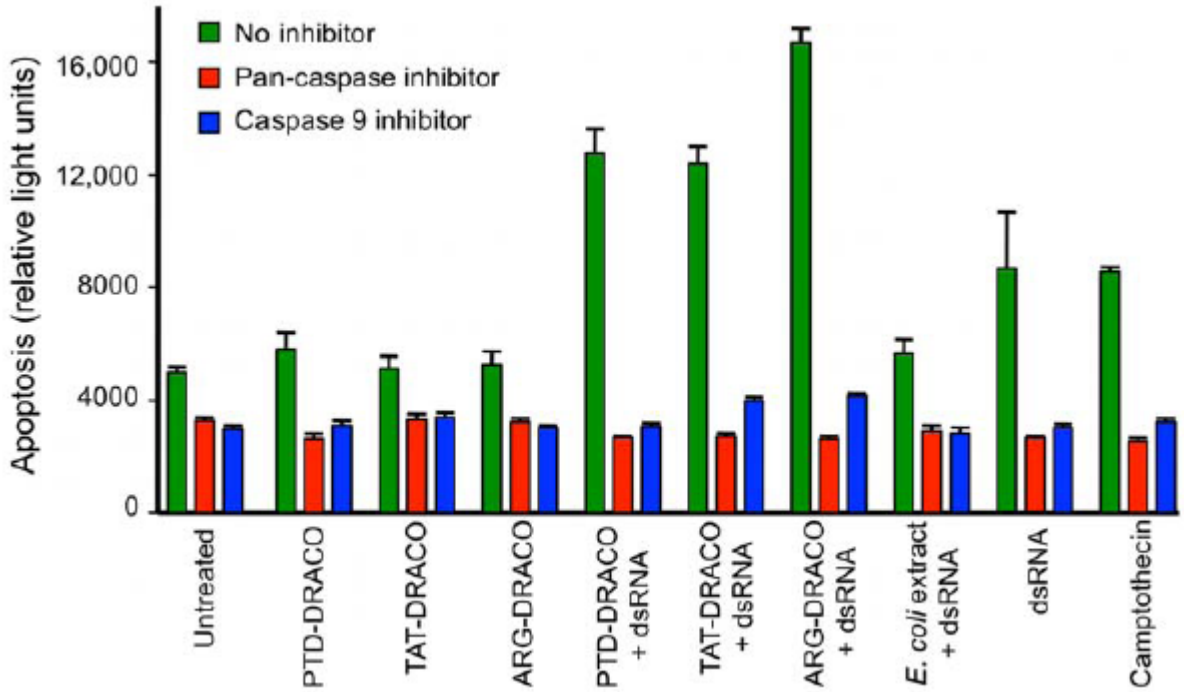


- DRACO proteins were synthesized by *E. coli* transfected with vectors containing these gene fusions
- Cells were collected and lysed and proteins were then purified using affinity chromatography for the His_6 tag
- Proteins were also equipped with either N or C terminal transduction tags which activate transfer into all cell types

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

DRACO: A New Approach to Antiviral Therapeutics

- In Vitro testing of DRACO indicates positive results under a variety test conditions

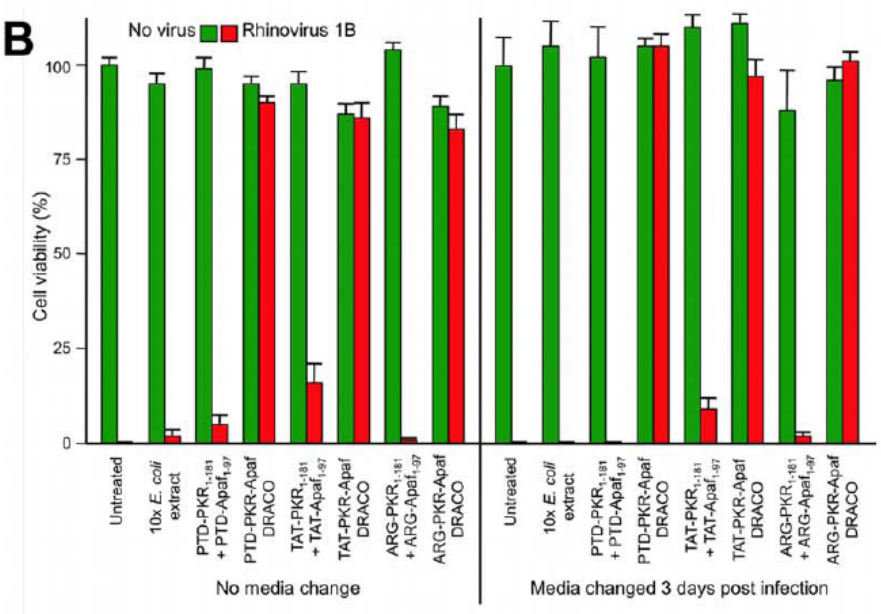


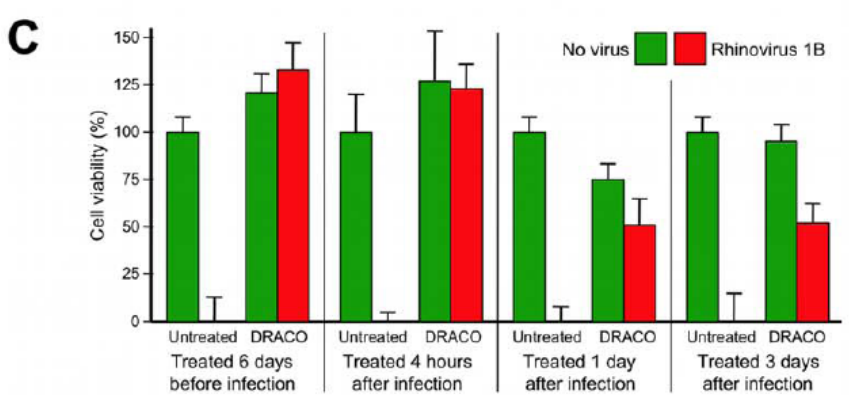
- Test uses a mouse cell line engineered to release light upon apoptotic death
- Increase in apoptotic death seen when both an active DRACO and dsRNA are added to a cell
- Negative controls using two types of caspase inhibitor show that the apoptotic affect is generated by the DRACO

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

DRACO: A New Approach to Antiviral Therapeutics

- In Vitro testing of DRACO indicates positive results under a variety test conditions



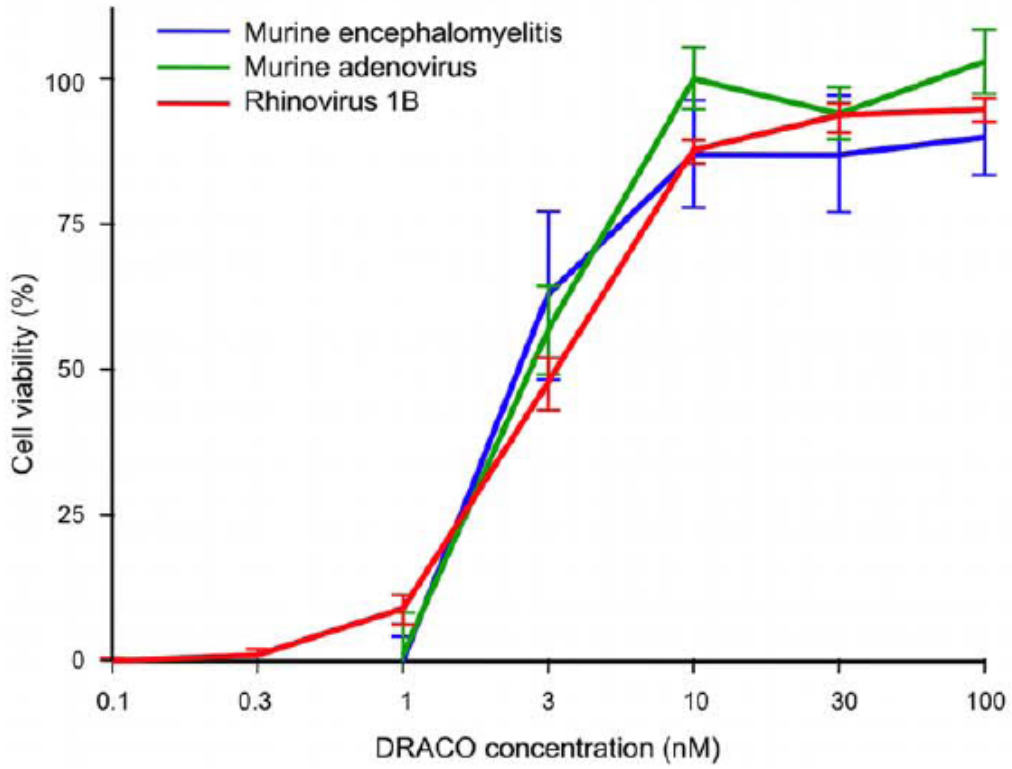


- Test uses normal human lung fibroblast cells (NHLF) grown in culture that is 100 nM in DRACO protein
- Figure B shows cells grown in culture containing active DRACO protein show almost complete viability when infected with rhinovirus 1B (common cold) whereas control cells are killed when infected
- Figure C shows viability of NHLF cells based on time of initiation of treatment with active DRACO protein

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

DRACO: A New Approach to Antiviral Therapeutics

- In Vitro testing of DRACO indicates positive results under a variety test conditions



- In vitro tests of NHLF cells against three different viruses show concentration curves centered at 3 nM
- Both rhinovirus 1B and encephalomyelitis are +sense ssRNA genomes (same as HIV)
- Adenovirus contains a dsDNA genome showing that the sensitivity of DRACO is possibly genome independent

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

DRACO: A New Approach to Antiviral Therapeutics

- In Vitro testing of DRACO indicates positive results under a variety test conditions

Table 1. We have demonstrated DRACO efficacy against a broad spectrum of viruses.

Virus	Family	Genome	Envelope	Replicates in	Species	Receptor
Rhinovirus 1B	Picornavirus	+ssRNA	No	Cytoplasm	Human	LDL receptor
Rhinovirus 2	Picornavirus	+ssRNA	No	Cytoplasm	Human	LDL receptor
Rhinovirus 14	Picornavirus	+ssRNA	No	Cytoplasm	Human	ICAM-1
Rhinovirus 30	Picornavirus	+ssRNA	No	Cytoplasm	Human	LDL receptor
Theiler's encephalomyelitis	Picornavirus	+ssRNA	No	Cytoplasm	Mouse	Sialic acid
Dengue type 2	Flavivirus	+ssRNA	Yes	Cytoplasm	Human	DC-SIGN, etc.
Influenza H1N1 A/PR/8/34	Orthomyxovirus	−ssRNA	Yes	Nucleus	Human	Sialic acid
Influenza H1N1 A/WS/33	Orthomyxovirus	−ssRNA	Yes	Nucleus	Human	Sialic acid
Tacaribe	Arenavirus	−ssRNA	Yes	Cytoplasm	Bat	Transferrin receptor 1
Amapari	Arenavirus	−ssRNA	Yes	Cytoplasm	Rodent	Transferrin receptor 1
Guama Be An 277	Bunyavirus	−ssRNA	Yes	Cytoplasm	Rodent	Unidentified
Guama Be Ar 12590	Bunyavirus	−ssRNA	Yes	Cytoplasm	Rodent	Unidentified
Reovirus 3	Reovirus	dsRNA	No	Cytoplasm	Human	Sialic acid
Adenovirus 5	Adenovirus	dsDNA	No	Nucleus	Human	CAR
Murine adenovirus	Adenovirus	dsDNA	No	Nucleus	Mouse	CAR

- Tests against fifteen different viral species show DRACO effective against all in vitro
- Tests against eleven different animal and human cell lines show DRACO effective in all against multiple viruses

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

DRACO: A New Approach to Antiviral Therapeutics

- In Vitro testing of DRACO indicates positive results under a variety test conditions

Table 2. We have demonstrated that DRACO is effective and nontoxic in a wide variety of cell types.

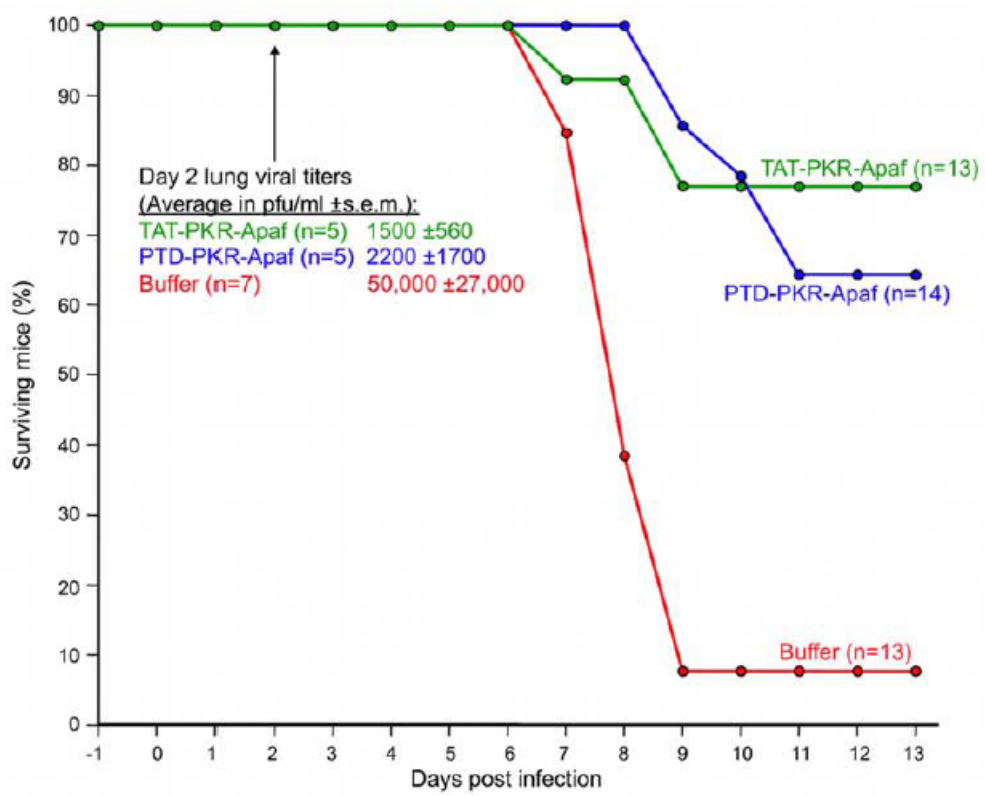
Cells	Species	Tissue	Immortalized	Viruses
Lung fibroblasts	Human	Lung	No	Rhino 1B, 2, 30; Flu 33, 34
Hepatocytes	Human	Liver	No	Rhino 1B, 2, 30; Flu 33, 34
Airway epithelial	Human	Trachea	No	Flu A/PR/8/34
Osteoblasts	Human	Bone	No	Rhino 1B, 2, 30; Flu 33, 34
Aortic muscle	Human	Heart	No	Rhino 1B, 2, 14, 30; Flu 33, 34
AD293	Human	Kidney	Yes	Adeno 5
H1-HeLa	Human	Cervix	Yes	Rhino 14
Vero E6	Monkey	Kidney	Yes	Amapari, Tacaribe, Guama, Dengue
L929	Mouse	Fibroblast	Yes	Enceph, MAdeno, Reo 3
BALB/3T3	Mouse	Fibroblast	Yes	Reo 3
NIH/3T3	Mouse	Fibroblast	Yes	Encephalomyelitis

- Tests against fifteen different viral species show DRACO effective against all in vitro
- Tests against eleven different animal and human cell lines show DRACO effective in all against multiple viruses

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572

DRACO: A New Approach to Antiviral Therapeutics

- In vivo testing of mice infected with H1N1 influenza virus show promise



- Mice were injected with DRACO from day –1 to day 3 once a day in fatty tissue
- Mice were then infected with 1.3 times the L_D50 dose of H1N1 influenza and survival rates were monitored

Rider, T. H. *et. al. PloS ONE* **2011**, *6*, e22572