Global Focus on Knowledge

From the Big Bang to a Green Planet: The 13.7-Billion-Year Journey of Matter

Dec. 3: Matter and Illness

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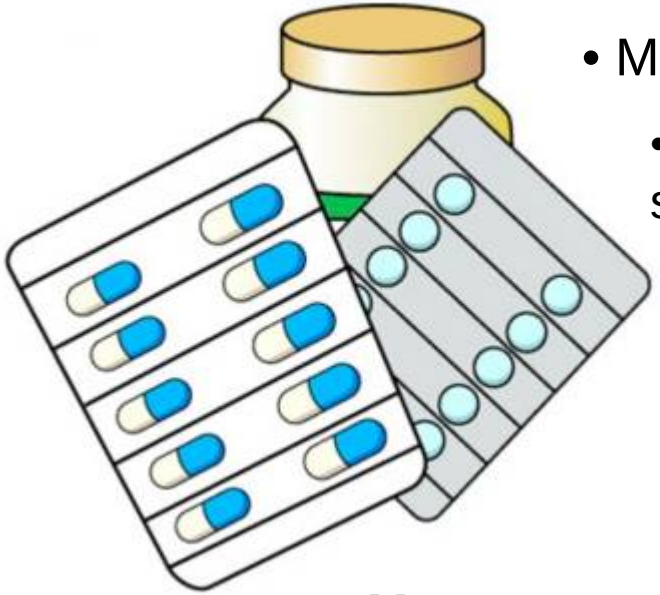
The University of Tokyo

Treating Illness with Pharmaceutical Substances



- Many pharmaceuticals are small organic compounds.
  - Some pharmaceuticals are derived from natural substances, and some are synthesized artificially.

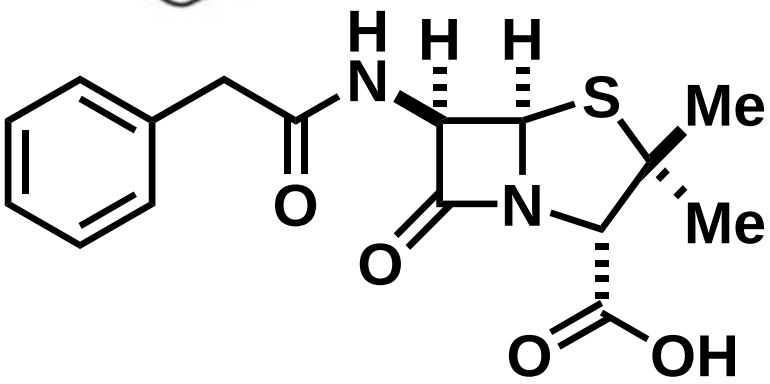
    While some natural substances are too highly toxic, others are insufficiently potent.

⇩

Many pharmaceutical substances are man-made designs that draw on potentially useful natural substances.

⇩

Pharmaceuticals must be designed with an understanding of biological mechanisms at the level of molecular matter.



The world's first antibiotic
Penicillin G (natural substance)

Pharmaceutical Substances and Treatment of Illnesses

How do pharmaceuticals work?
How are they designed?

1. Immunosuppressants enabling organ transplants

2. Antiviral agents

   The science of pharmaceuticals preventing the onset of AIDS

   The science of anti-influenza agents

3. The science of pharmaceuticals for treating high blood pressure

4. The science of pharmaceuticals for treating hyperlipemia

The Science of Pharmaceuticals
Enabling Organ Transplants

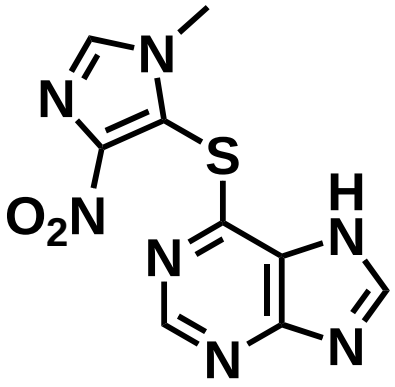
Rejection prompted by the body's defense mechanism (immune response) — Check — Immunosuppressant

1954: World's first organ transplant (kidney) between identical twins

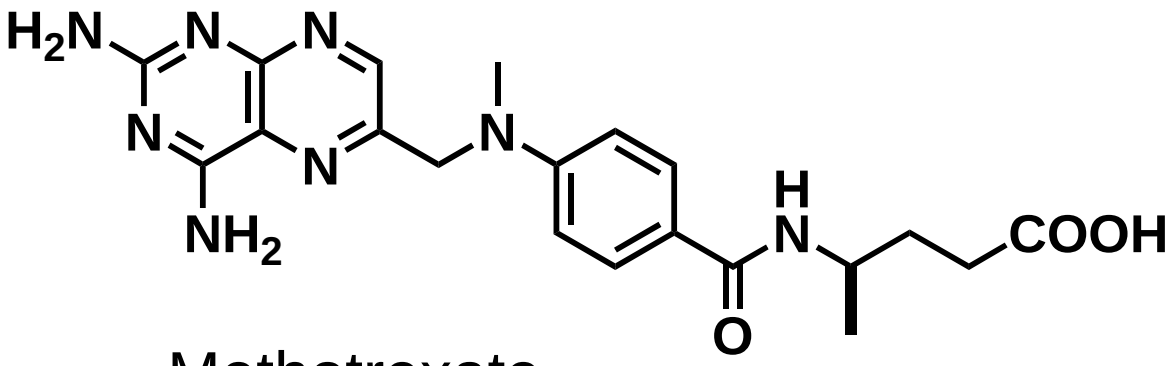
Joseph E. Murray and E. Donnal Thomas

(1990 Nobel Prize in Physiology or Medicine)

1962: Kidney transplant between unrelated humans with immunosuppressants



Azathioprine



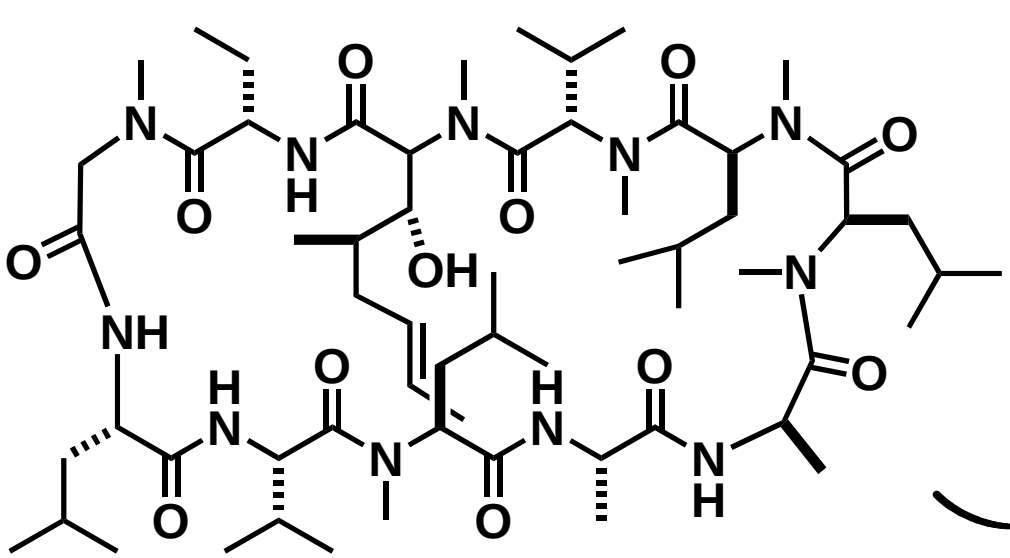
Methotrexate

1963: Liver transplant, lung transplant

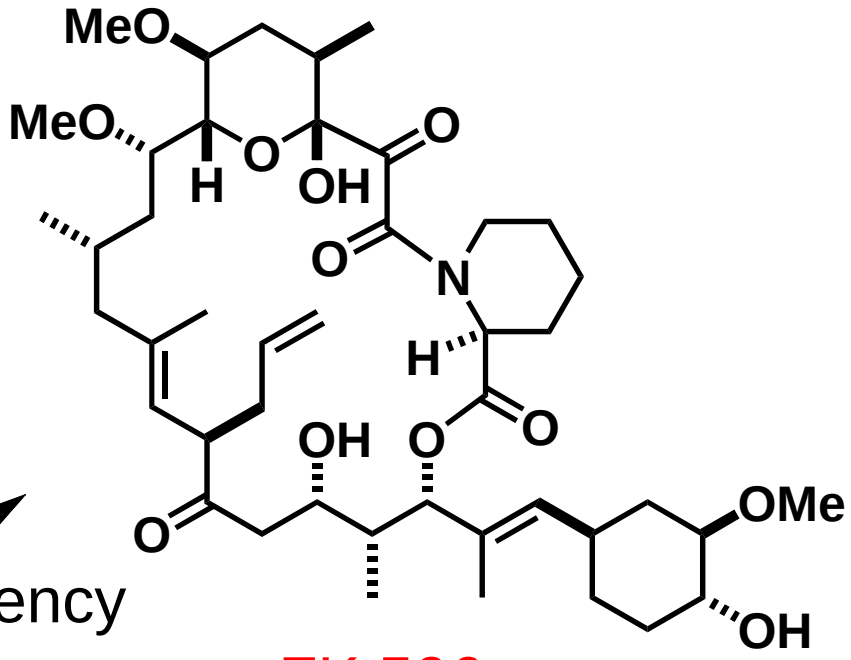
1967: Heart transplant

The Science of Pharmaceuticals
Enabling Organ Transplants

Discovery of a selective and powerful immune-system T-cell activation inhibitor



100x potency



Cyclosporine A

Sandoz, 1971

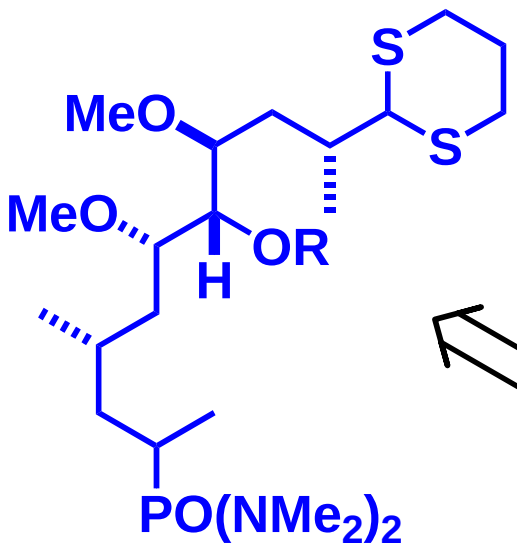
FK 506

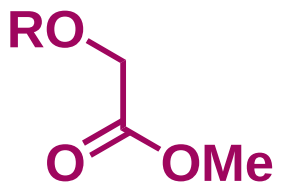
Fujisawa, 1987

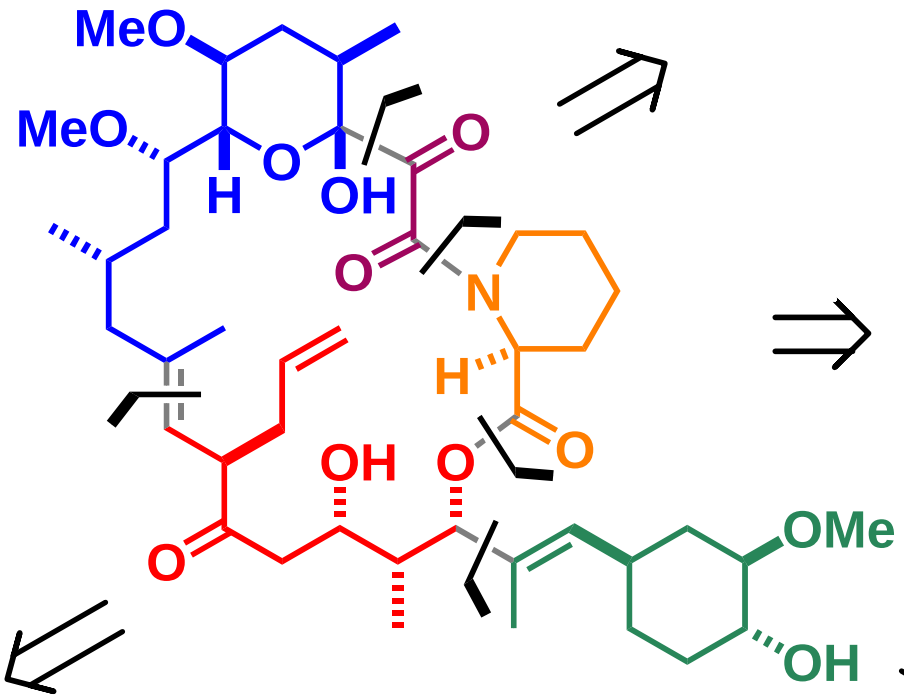
aka Tacrolimus

(Tsukuba macrolide immunosuppresant)

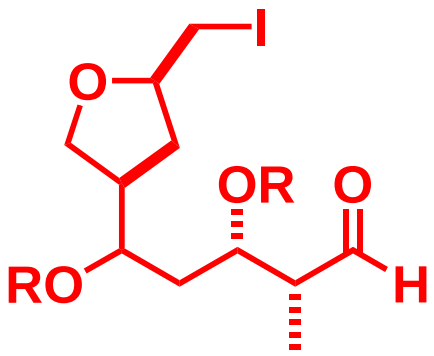
Pure Chemical Synthesis of FK 506

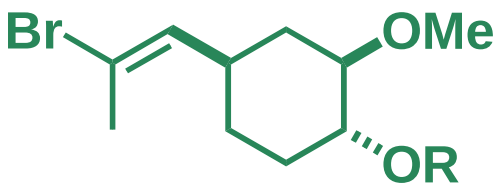




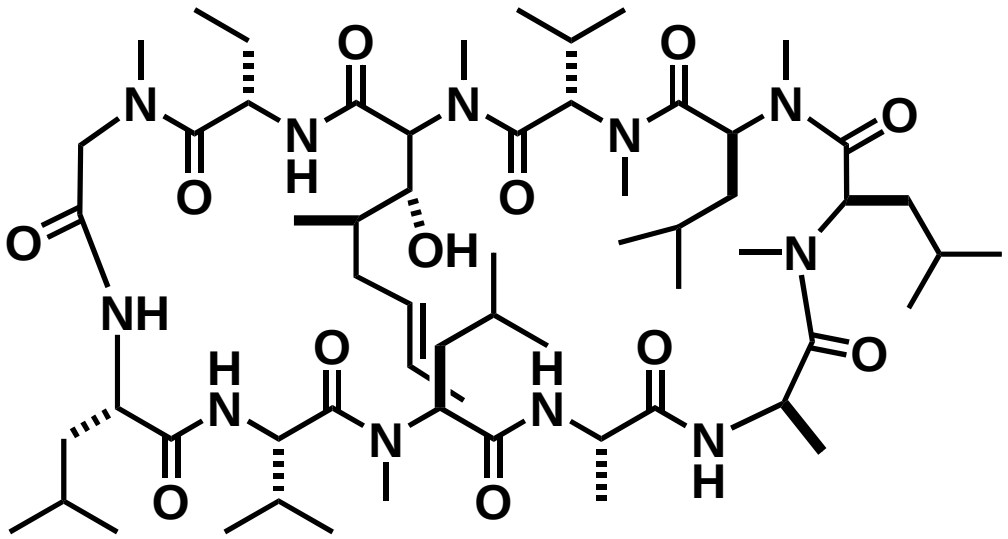


FK 506

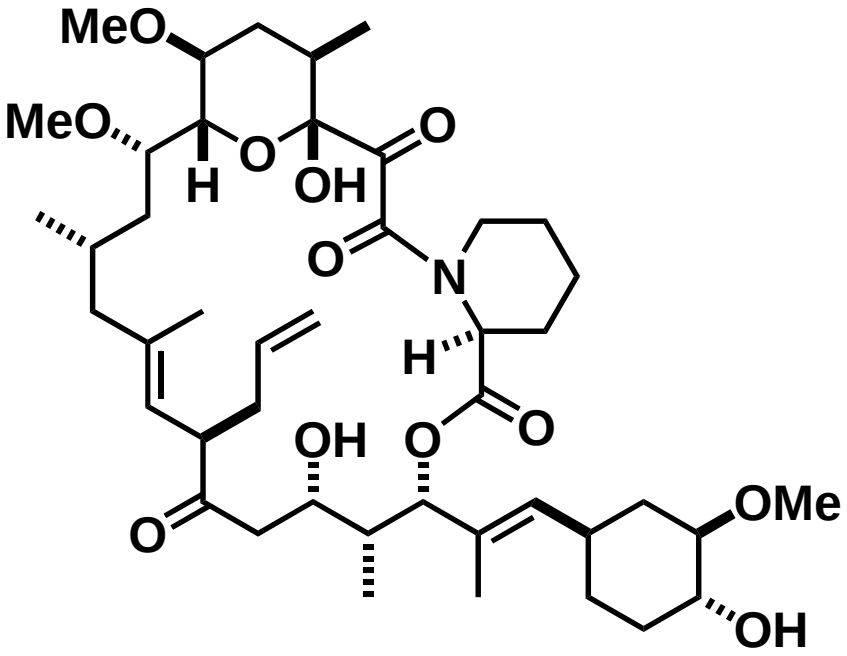




Chemical Biology Instigated by Immunosuppressant Research



Cyclosporine A

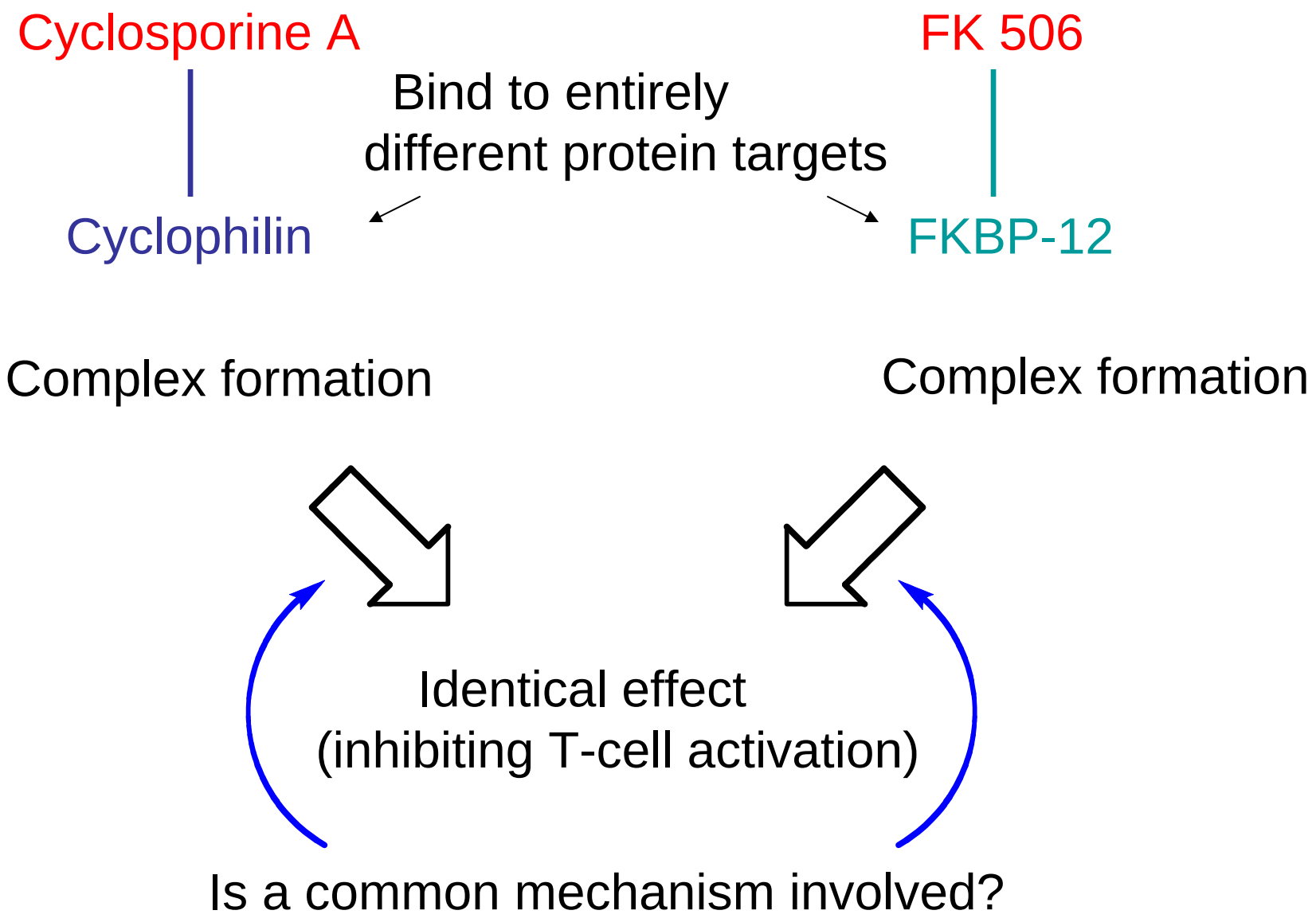


FK 506

Entirely different structures ⇨ Identical effect (inhibiting T-cell activation)

What mechanism?

Chemical Biology Instigated by Immunosuppressant Research



Chemical Biology Instigated by Immunosuppressant Research

Rapamycin also
binds to FKBP-12

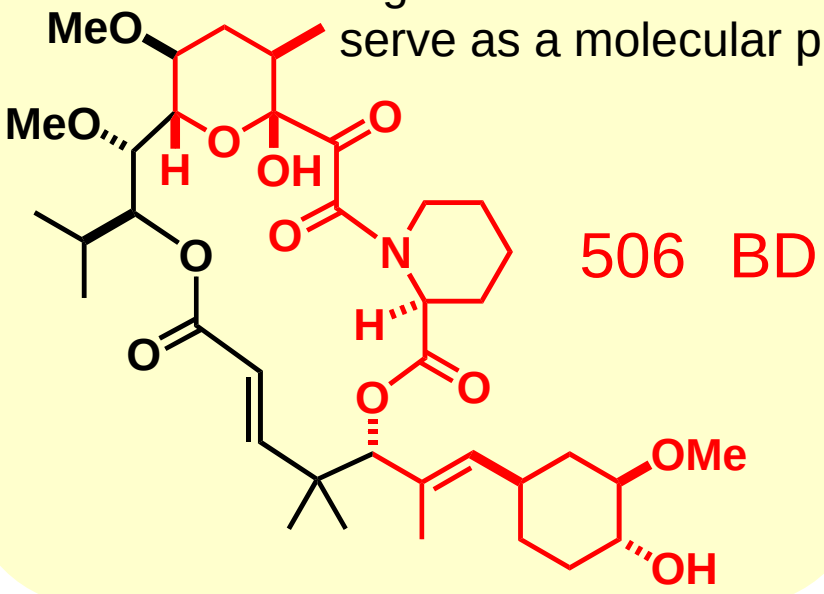
⇩

Identical behavior
(inhibiting T-cell activation)

Rapamycin — FKBP-12

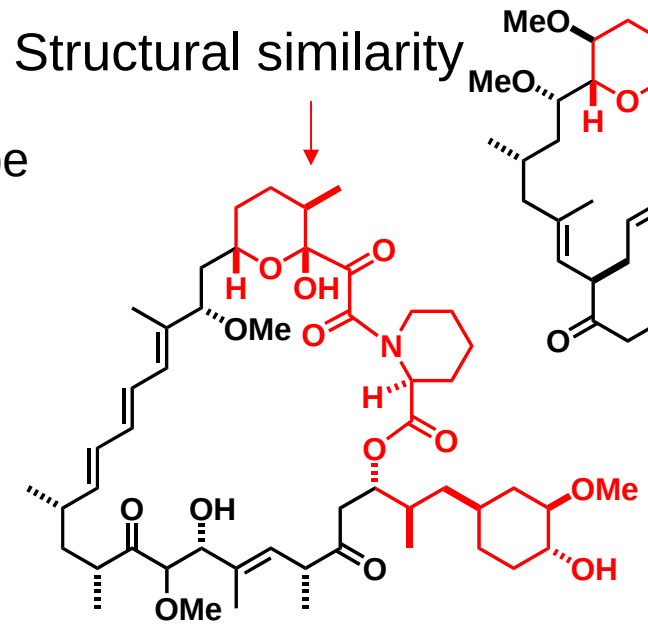
FK 506 — FKBP-12

Chemically synthesized artificial molecule retaining a common site to serve as a molecular probe

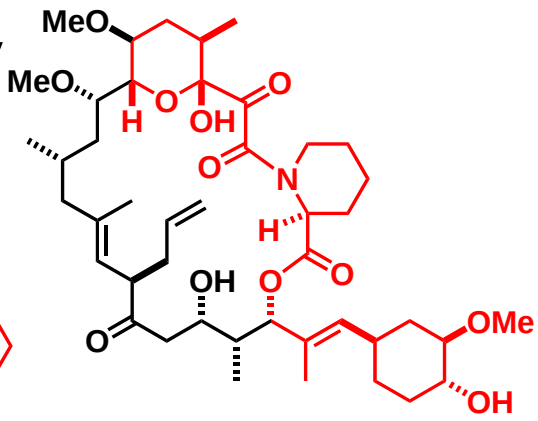


506 BD

Structural similarity



Rapamycin



FK 506

Chemical Biology Instigated by Immunosuppressant Research

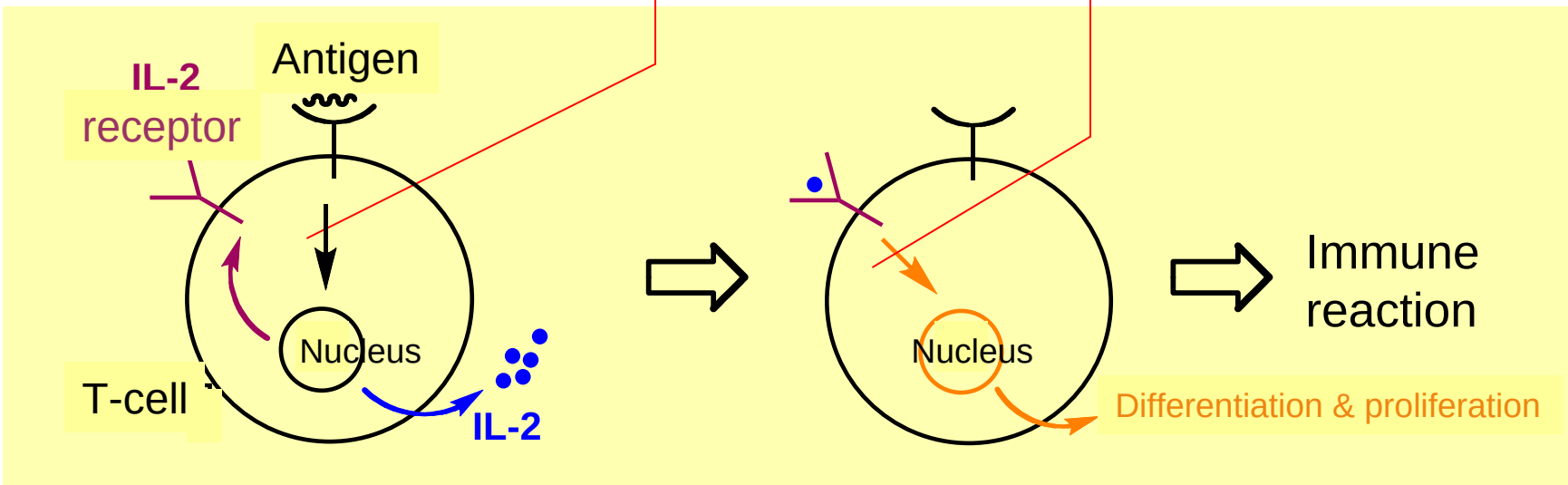
Form the complexes

506 BD–FKBP-12 ⇨ No action

Rapamycin–FKBP-12 ⇨ Inhibits reaction to interleukin-2 (IL-2) ⇨

FK 506–FKBP-12 ⇨ Inhibits production of interleukin-2 (IL-2) ⇨

Identical effect:
Inhibiting T-cell activation



Chemical Biology Instigated by Immunosuppressant Research

Form the complexes

506 BD–FKBP-12 ⇨ No action (**Unable to bind to calcineurin**)

Rapamycin–FKBP-12 ⇨ Inhibits reaction to interleukin-2 (IL-2) ⇨

FK 506–FKBP-12 ⇨

Cyclosporine A –cyclophilin ⇨

Inhibits production of interleukin-2 (IL-2) ⇨

Identical effect: Inhibiting T-cell activation

⇧

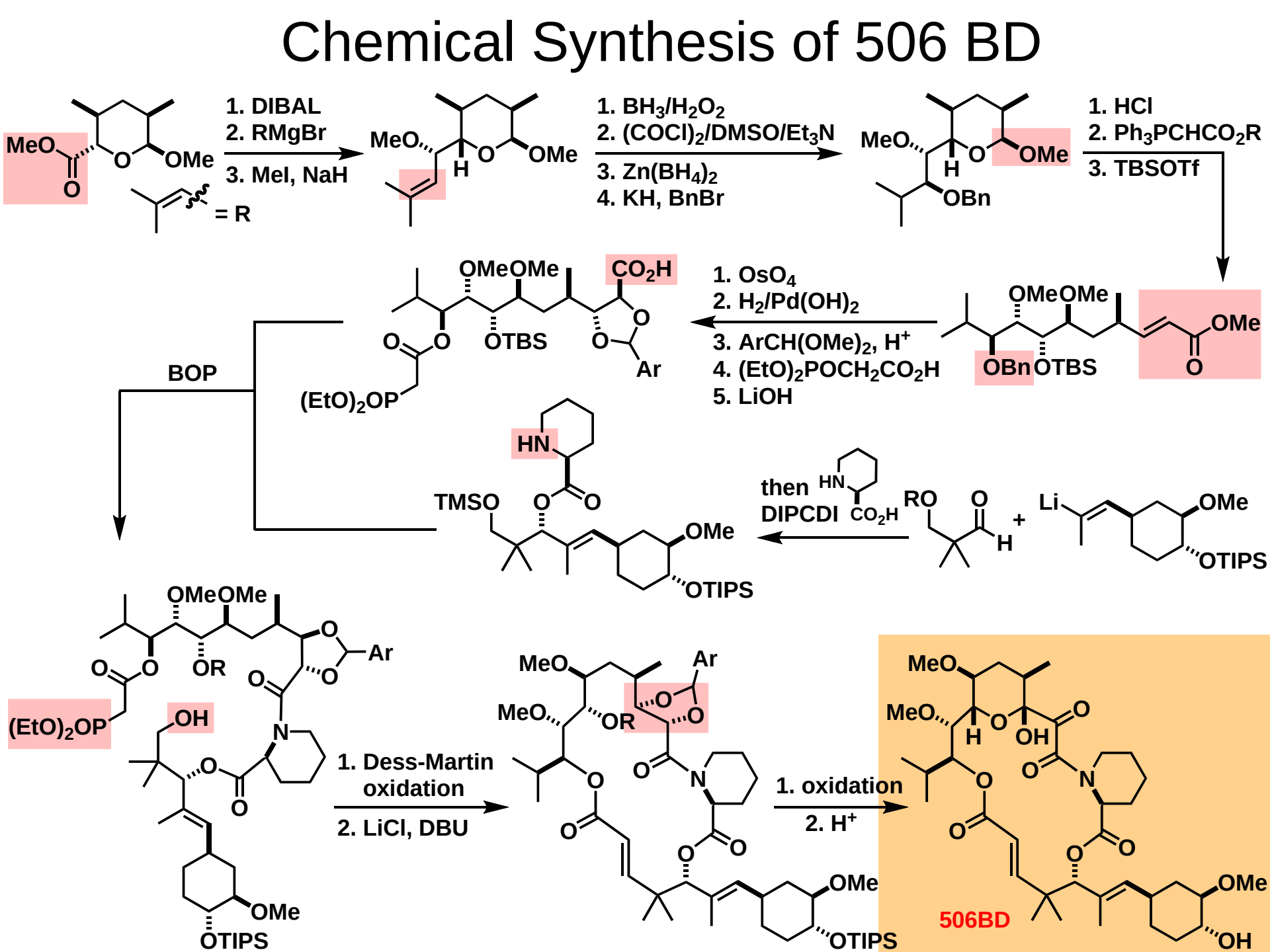
Each molecule forms a complex

Common target protein in calcineurin ⇘

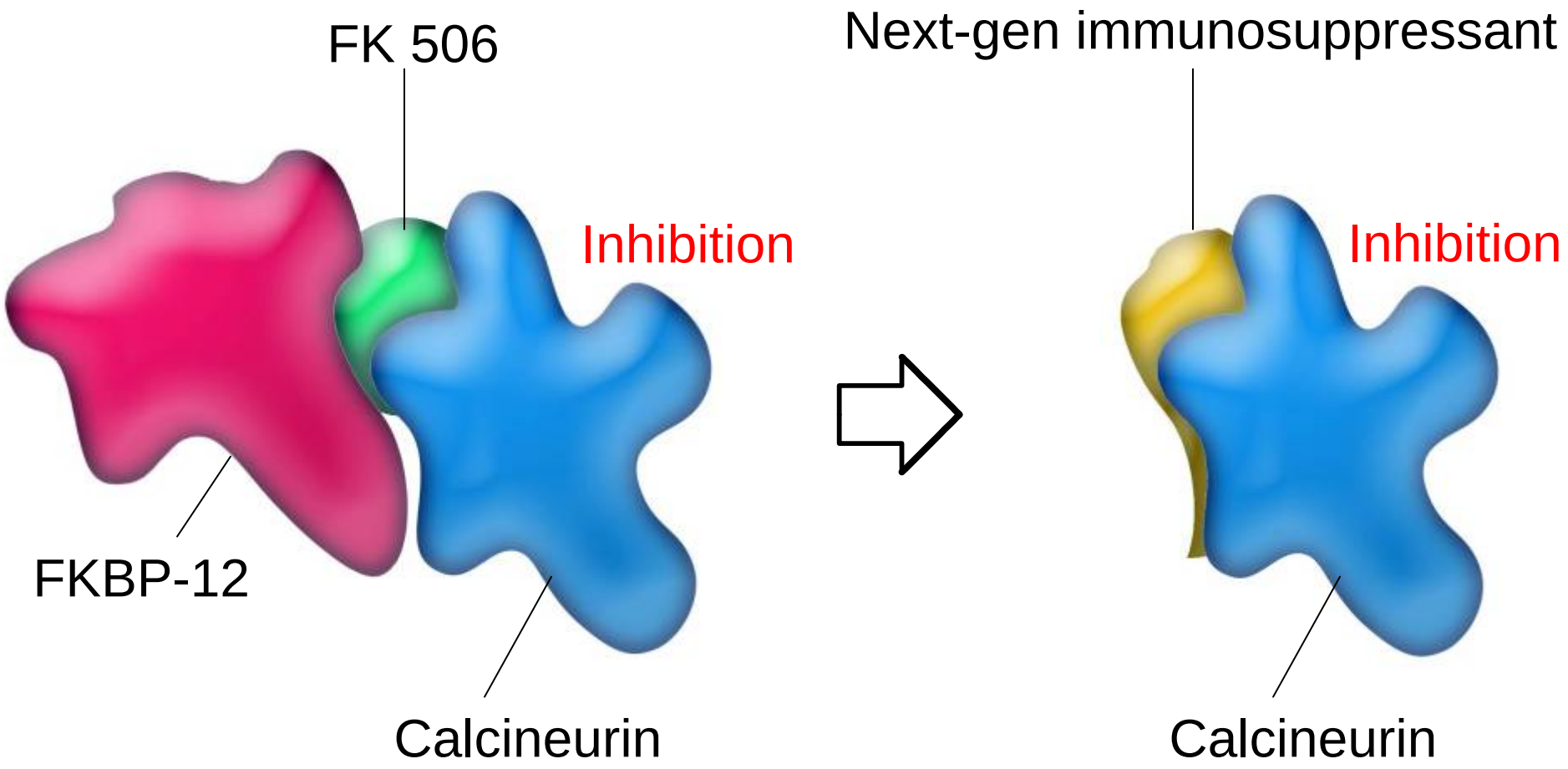
FK 506–FKBP-12–calcineurin

Cyclosporine A–cyclophilin–calcineurin

Chemical Synthesis of 506 BD



Design of Immunosuppressants to Serve the Future



The Science of Pharmaceuticals Preventing the Onset of AIDS

AIDS: Acquired Immune Deficiency Syndrome

HIV: Human Immunodeficiency Virus

Montagnier and Barré-Sinoussi identified HIV in AIDS patients at the Pasteur Institute in 1983

(2008 Nobel Prize in Physiology or Medicine)

HIV infection does not result in the immediate onset of AIDS.

Upon infiltrating the human body, HIV infects the CD4-positive T-cells that play an important part in the human immune system, leading to the propagation of HIV and a fall in the T-cell count.

After a long period of incubation, the steep decline in the T-cell count results in impaired immunity and opportunistic infections.

Inhibiting HIV Propagation

Keeping HIV propagation under control is an effective way of preventing the onset of AIDS. HIV is a highly mutable virus: Even if a vaccine were developed for it, variants of HIV would soon appear on which the vaccine does not work.

Vaccine : A substance that recognizes the surface structure specific to a virus

⇩

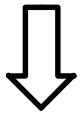
That HIV is quick to change its surface structure makes it an unpromising candidate for vaccine treatment

⇩

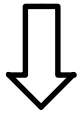
We must discover the mechanism of viral propagation and develop a drug to disrupt the logic of that propagation

Design Guidelines for an HIV Drug

Unlike bacteria, viruses are unable to propagate on their own. They parasitize human or other host cells and use the cells' mechanisms of DNA replication and protein production to propagate explosively.

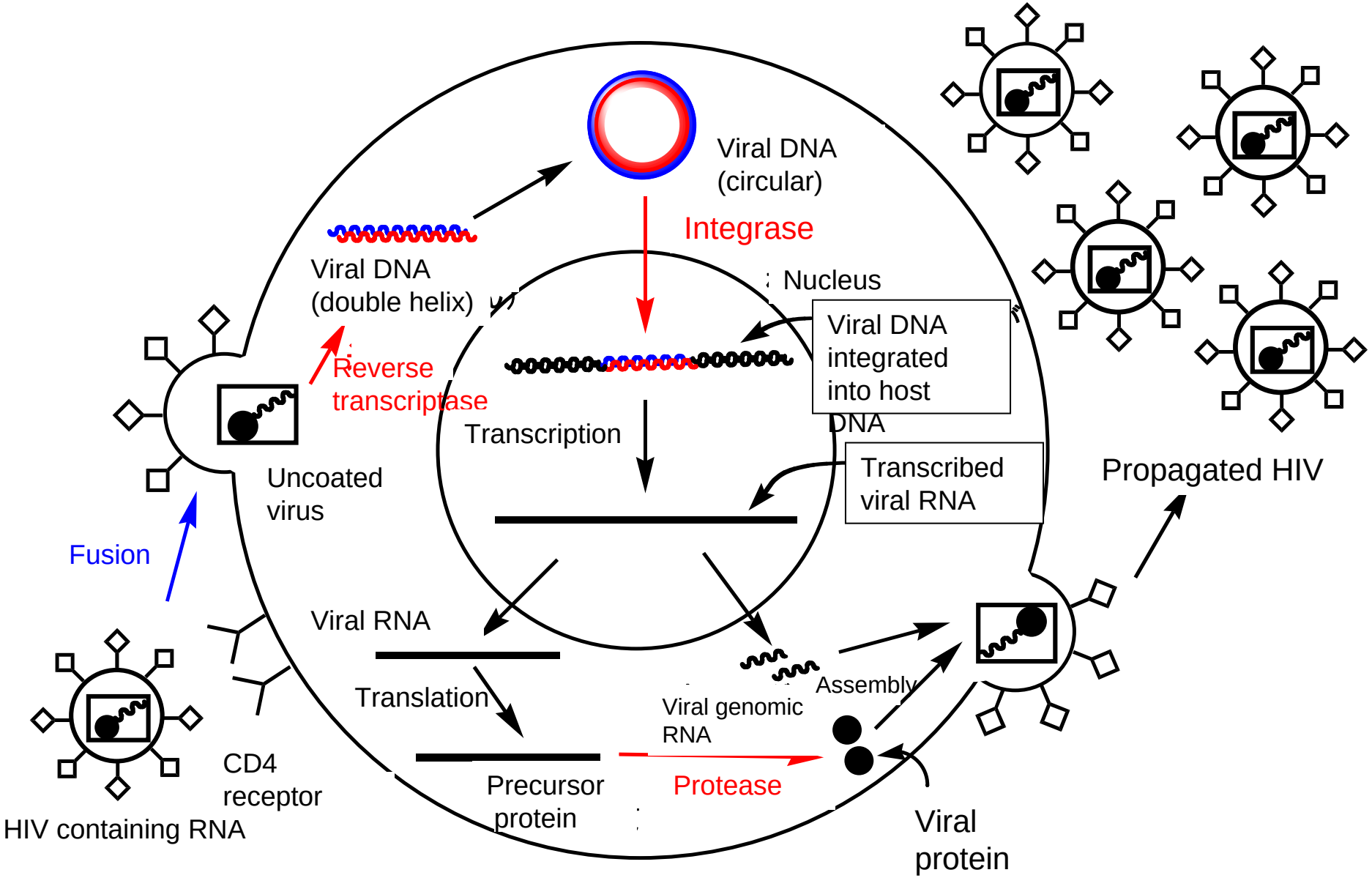


The design strategy for an anti-viral agent is fundamentally different from that for an antibiotic that will attack bacterial cells proper.



Pharmaceutical design must avoid inhibiting natural human biological functions and instead selectively attack only the propagation mechanisms specific to HIV, the flu virus and other viruses.

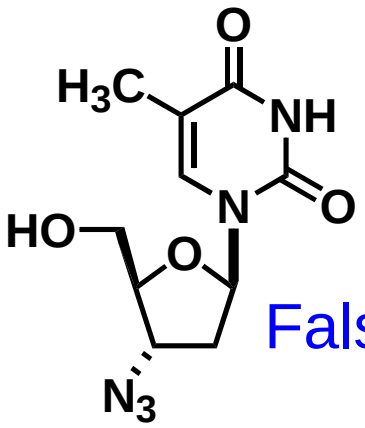
The HIV Propagation Mechanism



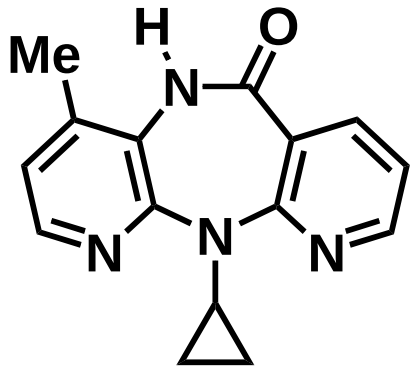
Possible HIV Drugs 1/4

Reverse transcriptase inhibitors:

HIV is a retrovirus that uses RNA to transmit its genetic information. In order to use the mechanisms of human cells to propagate, it must use reverse transcriptase to convert it to the same DNA structure as that of humans.



False nucleic acid



Bonds to site of enzyme activity

AZT (1987) -- World's first HIV drug
Nucleoside reverse transcriptase inhibitor

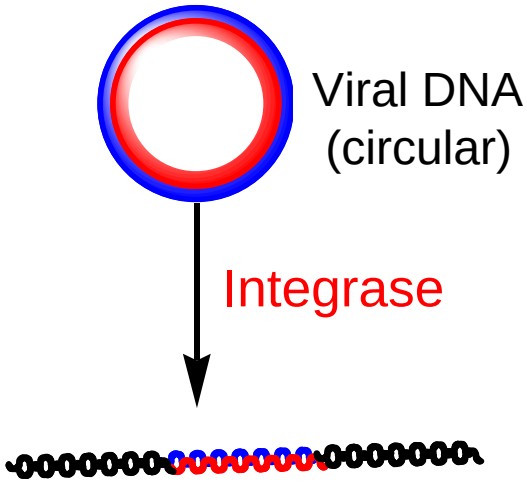
Nevirapine (1996)
Non-nucleoside reverse transcriptase inhibitor

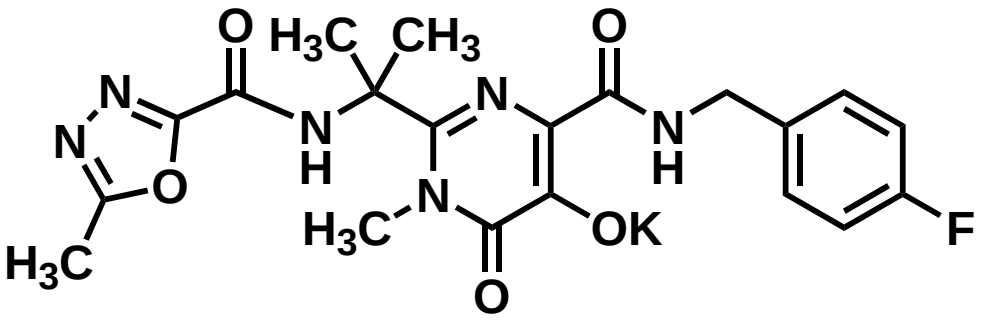
HIV is unable to propagate if reverse transcriptase is blocked.

Possible HIV Drugs 2/4

Integrase inhibitors:

Viral DNA integrates with human DNA by means of its enzyme integrase. The viral DNA then uses the mechanisms of human cells to propagate. Integrase works by chopping up human DNA and inserting viral DNA in the openings to join it up again the way you would edit videotape.





Raltegravir potassium

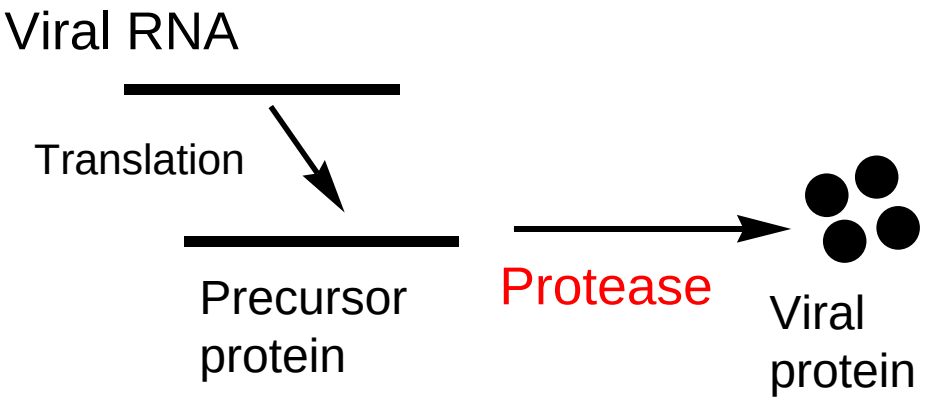
（Released to market Sept. 2007, available in Japan July 2008）

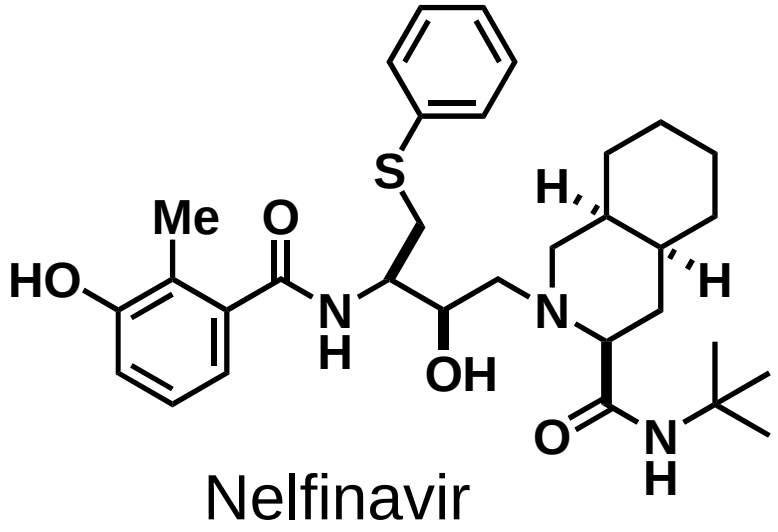
HIV is unable to propagate if integrase is blocked.

Possible HIV Drugs 3/4

Protease inhibitors:

HIV replication is enabled by the conversion of viral protein precursors synthesized inside human cells to viral proteins by the enzyme protease.





Nelfinavir

Many protease inhibitors have reached market since 1995

HIV is unable to propagate if protease is blocked.

Possible HIV Drugs 4/4

Fusion inhibitors ：

These agents prevent the step of HIV fusion with CD4-positive T-cells.

Currently in clinical trials in Japan.

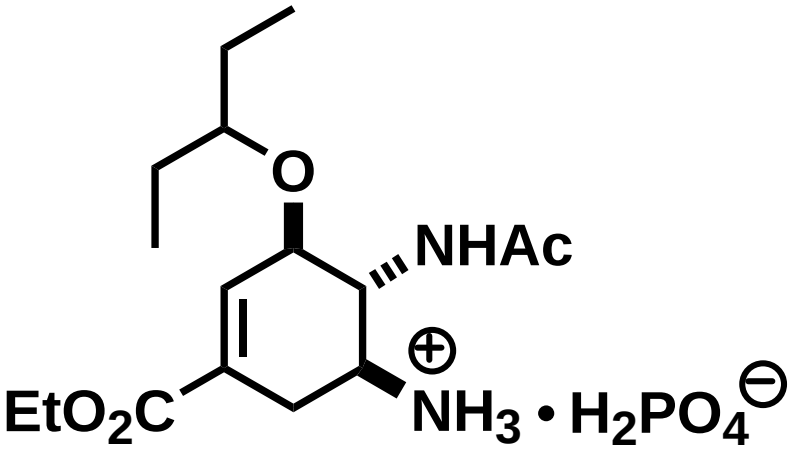
Treating HIV

（HAART：Highly Active Anti-Retroviral Therapy）:

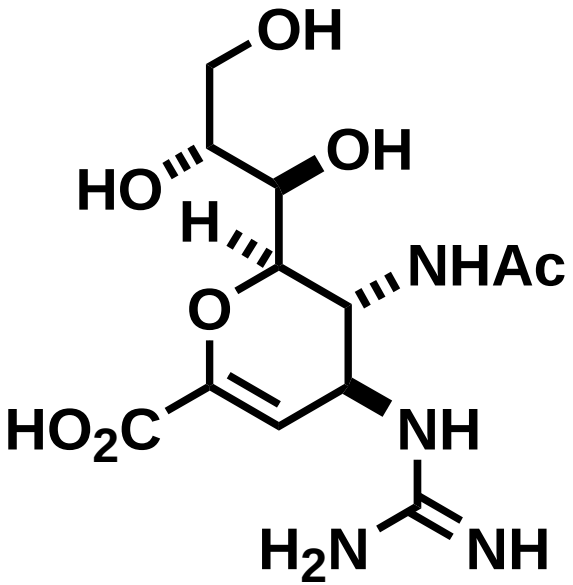
Since HIV is highly mutable, treatment with a single drug results in the emergence of resistant variants of the virus. Using multiple drugs that operate by different mechanisms in combination permits effective checking of HIV propagation and prevention of the onset of AIDS over an extended period. Such courses of treatment are also called combinatorial therapies or cocktail therapies.

Unfortunately, however, no treatment or pharmaceutical has yet been found that purges HIV from the body.

The Science of Pharmaceuticals for Pandemic Influenza

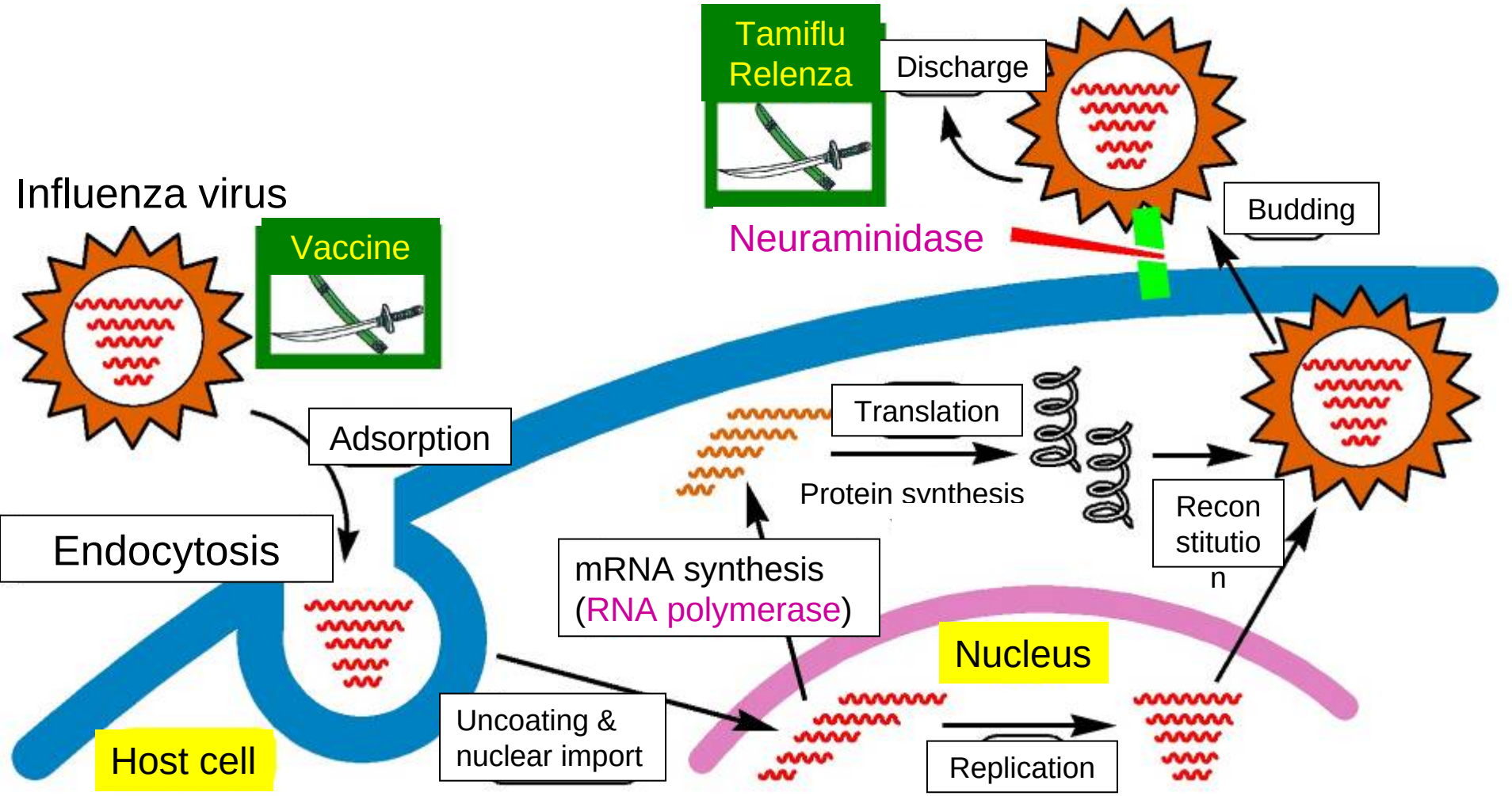


Tamiflu

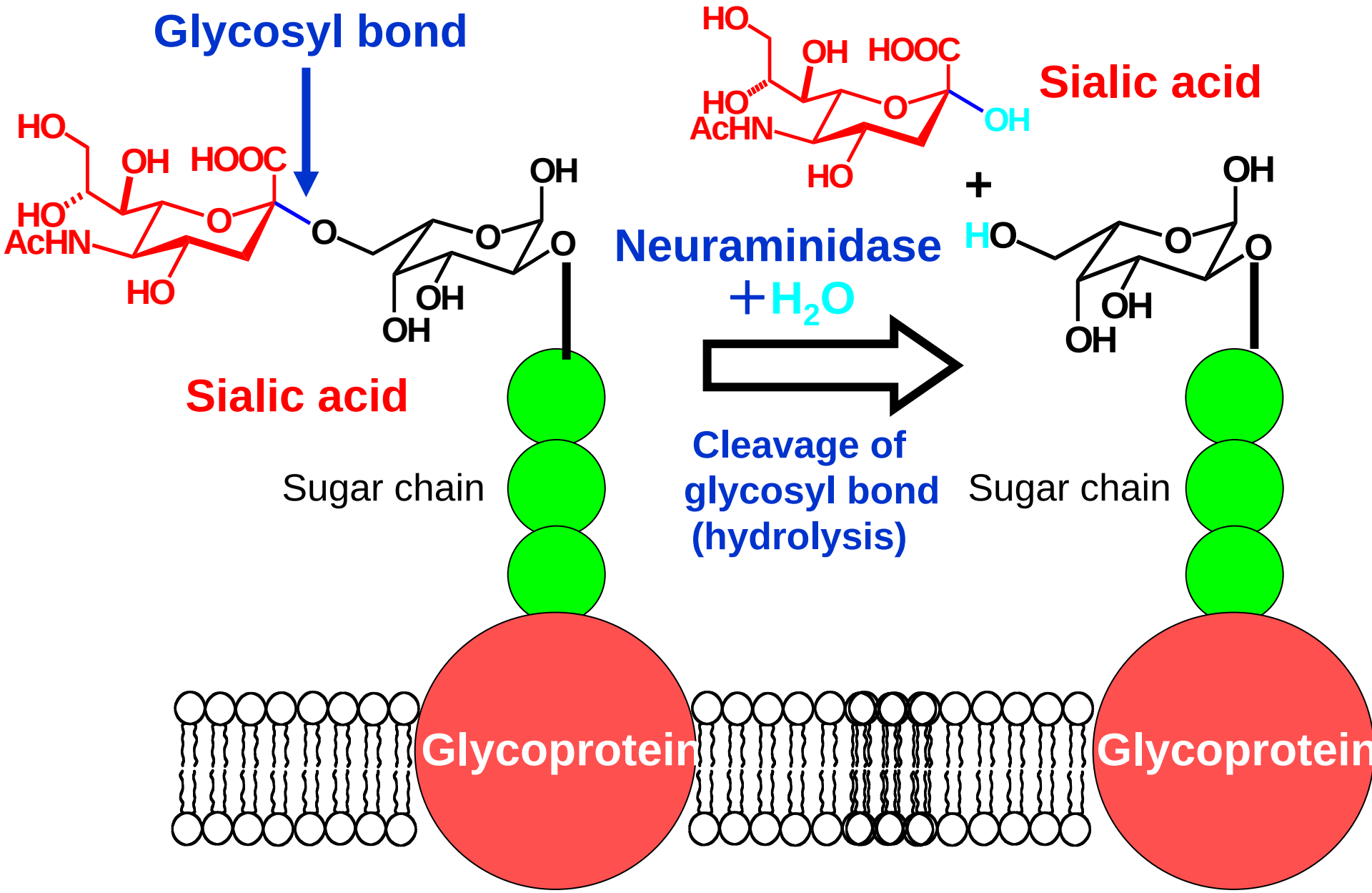


Relenza

Life Cycle of the Influenza Virus

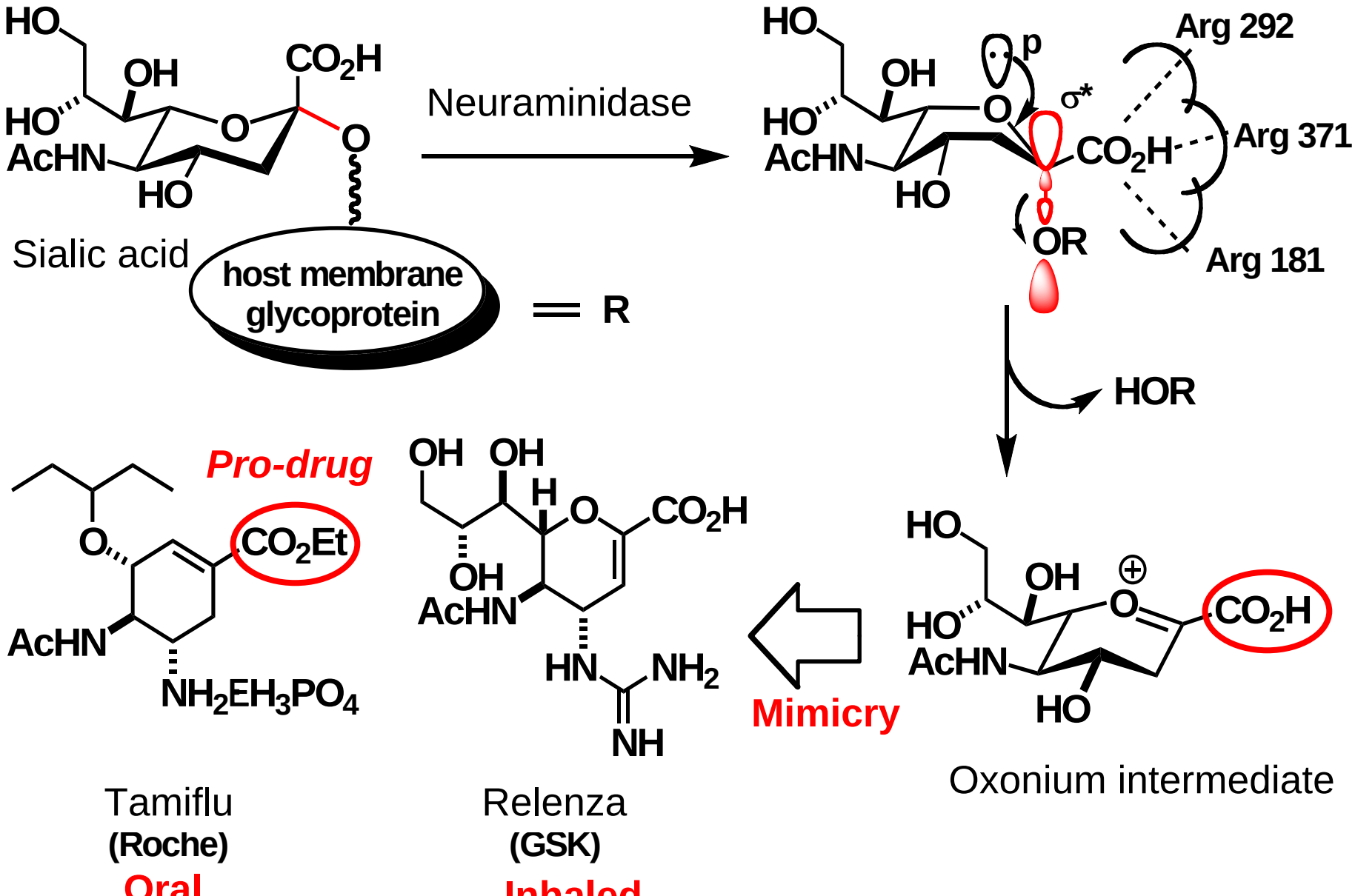


How Neuraminidase Works

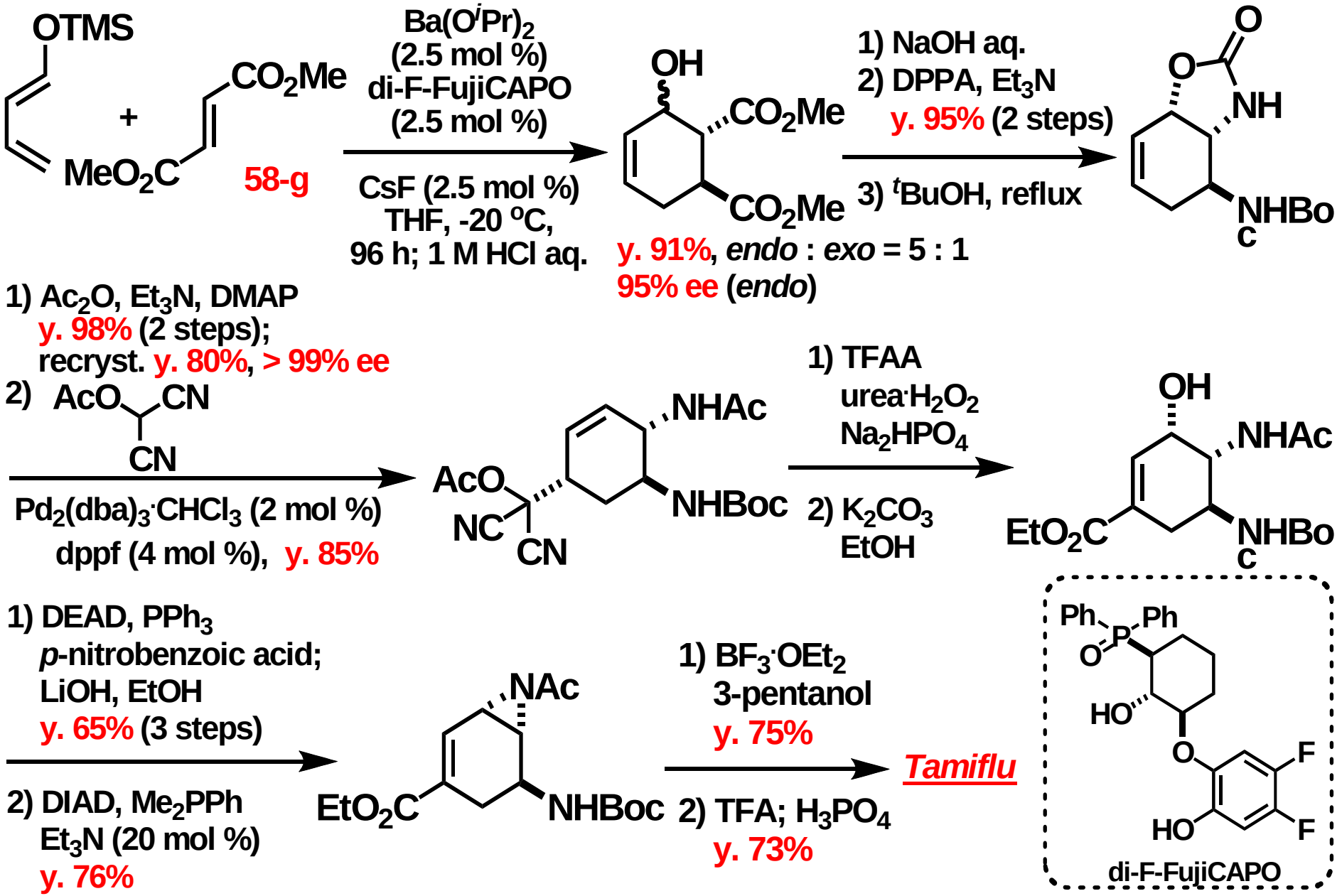


Molecular Design of a Neuraminidase Inhibitor

Kim, C. U. *et al. J. Am. Chem. Soc.* 1997, *119*, 681.



Working Towards a Stable Global Supply of Tamiflu



Yamatsugu, K.; Yin, L.; Kamijo, S.; Kimura, Y.; Kanai, M.; Shibasaki, M. Angew. Chem. in press.

The Emergence of Tamiflu-Resistant Strains and the Importance of Relenza

Although the mutation of histidine to tyrosine at position 274 in neuraminidase reduces its binding affinity to Tamiflu to one in c.270, its binding affinity to Relenza falls only to one in two. In other words, Relenza remains effective against Tamiflu-resistant strains.

Figures inserted here omitted for reasons of copyright.

***Nature* 2008, *453*, 1258**.