Structural Virology

Lecture 10

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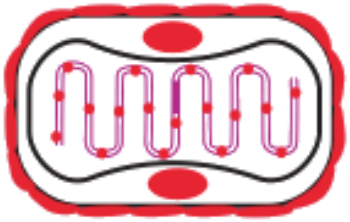
NÁRODNÍ PLÁN OBNOVY
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY

Virus vaccines

Live attenuated virus		Polio (Sabin)
Inactivated virus		Polio (Salk)
Virion subunit		Influenza (haemagglutinin and neuraminidase)
Live recombinant virus		Rabies (for wildlife vaccination)
Virus-like particles		Hepatitis B
DNA		SARS coronavirus (experimental)

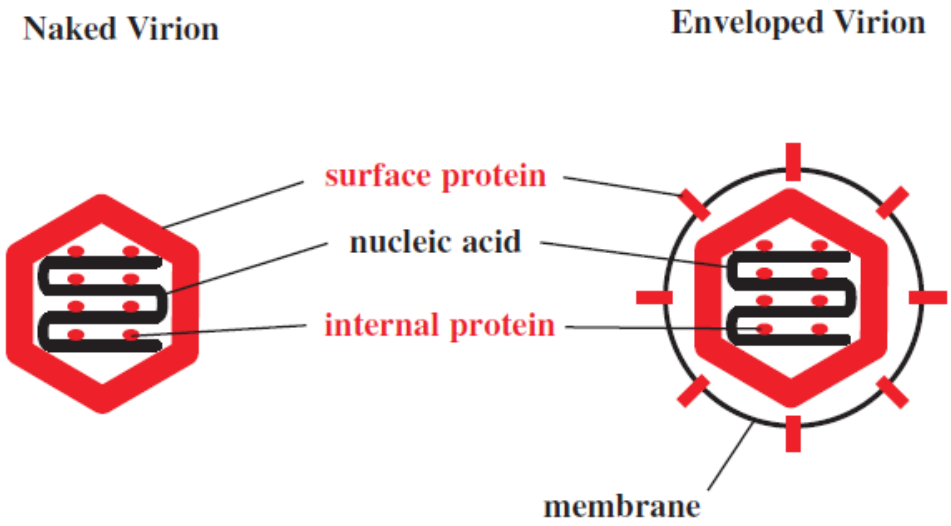
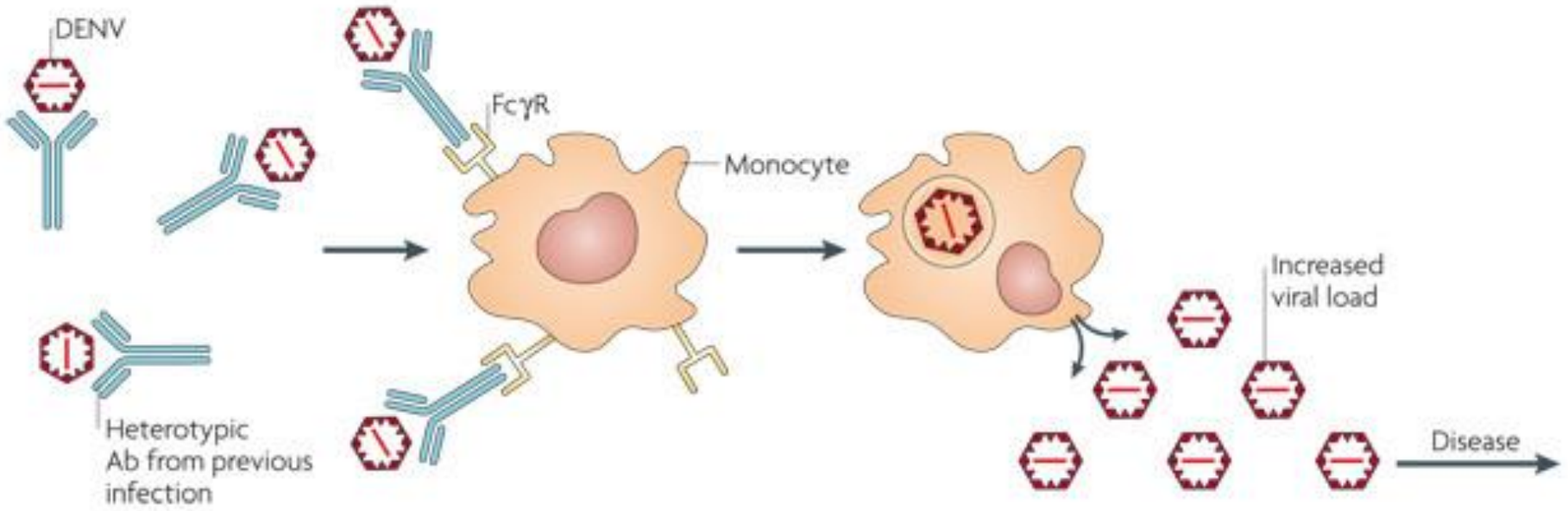
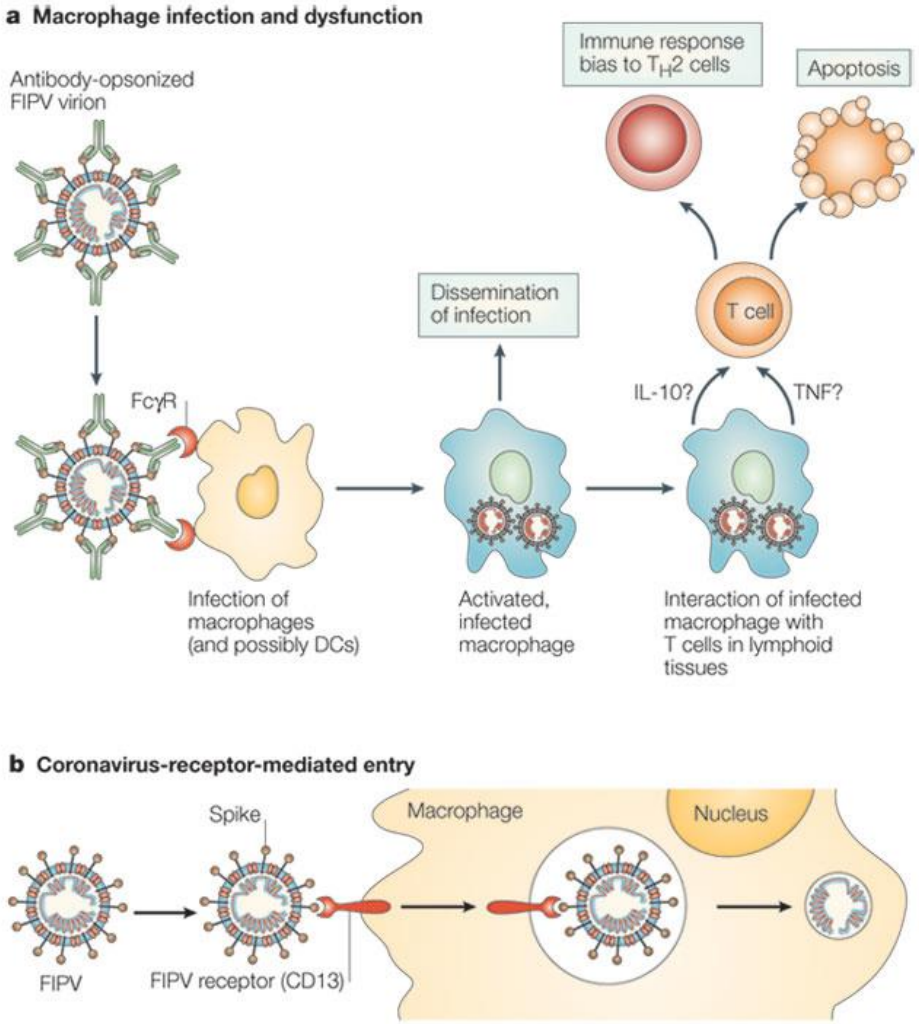


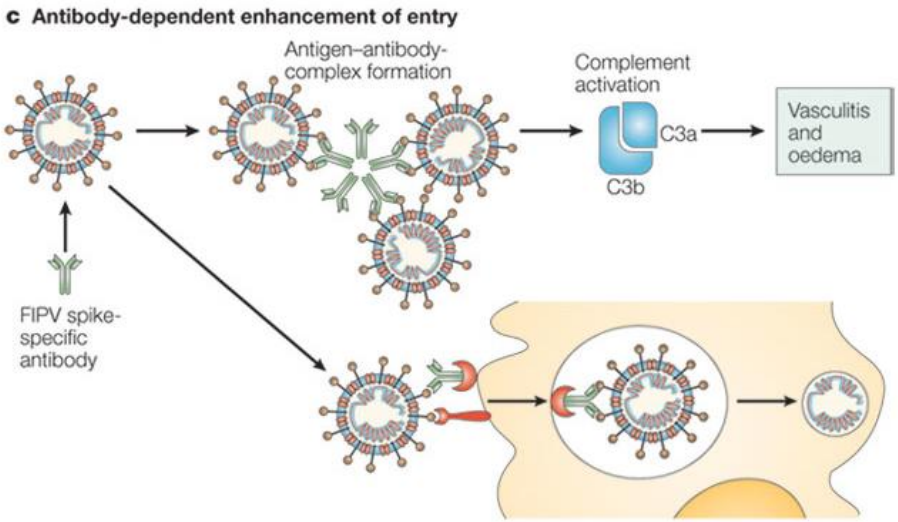
Figure 24.1 **Inactivation targets in virions.** Infectivity of a virion may be destroyed by damage to a nucleic acid, a protein, and/or a lipid membrane. Alteration of a surface protein might prevent a virion from attaching to its host cell and/or from entering the cell. Stripping the envelope from an enveloped virion removes the surface proteins and achieves the same outcome. Alteration of internal proteins can destroy properties, such as enzyme activities, essential for the replication of the virus.

Antibody dependent enhancement dengue



Antibody dependent enhancement - coronaviruses





Smallpox

- killed an estimated 400,000 Europeans annually during the 18th century.
- was responsible for a third of all blindness.
- of those infected, 20–60%—and over 80% of infected children—died
- responsible for an estimated 300–500 million deaths during the 20th century

Vaccine Types

- Attenuated viruses
- Inactivated viruses
- Virion subunits
- Recombinant viruses
- Virus-like particles
- Synthetic peptides
- DNA vaccines

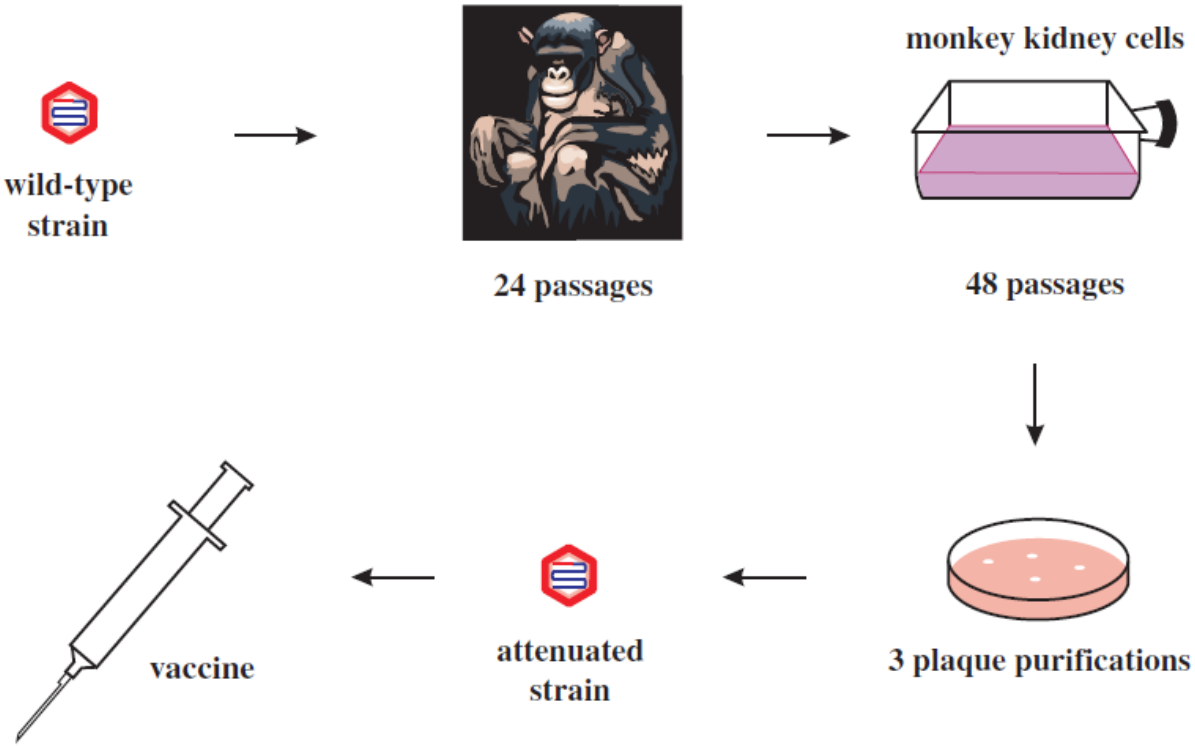


Figure 25.1 Derivation of attenuated poliovirus strain (Sabin type 1) from wild-type poliovirus strain (Mahoney 1).

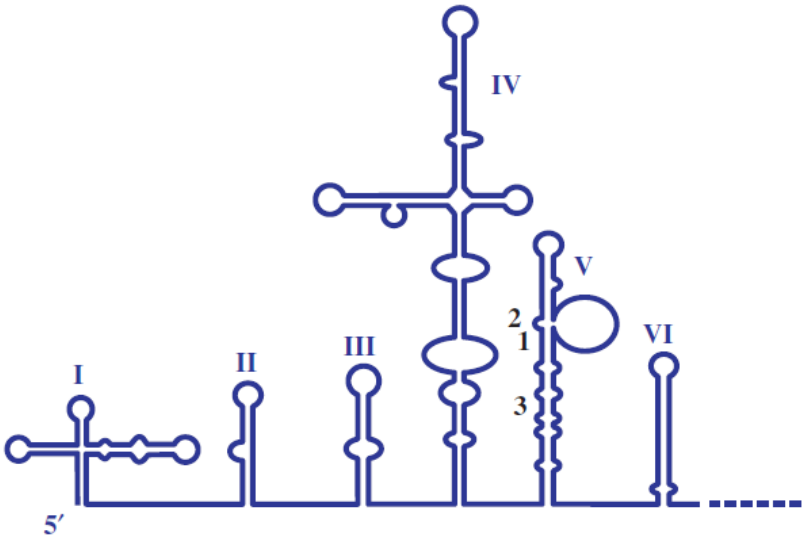


Figure 25.2 5′ end of poliovirus RNA with expanded view of domain V. For each of the three Sabin strains a mutation in domain V that contributes to the attenuation of neurovirulence is indicated.

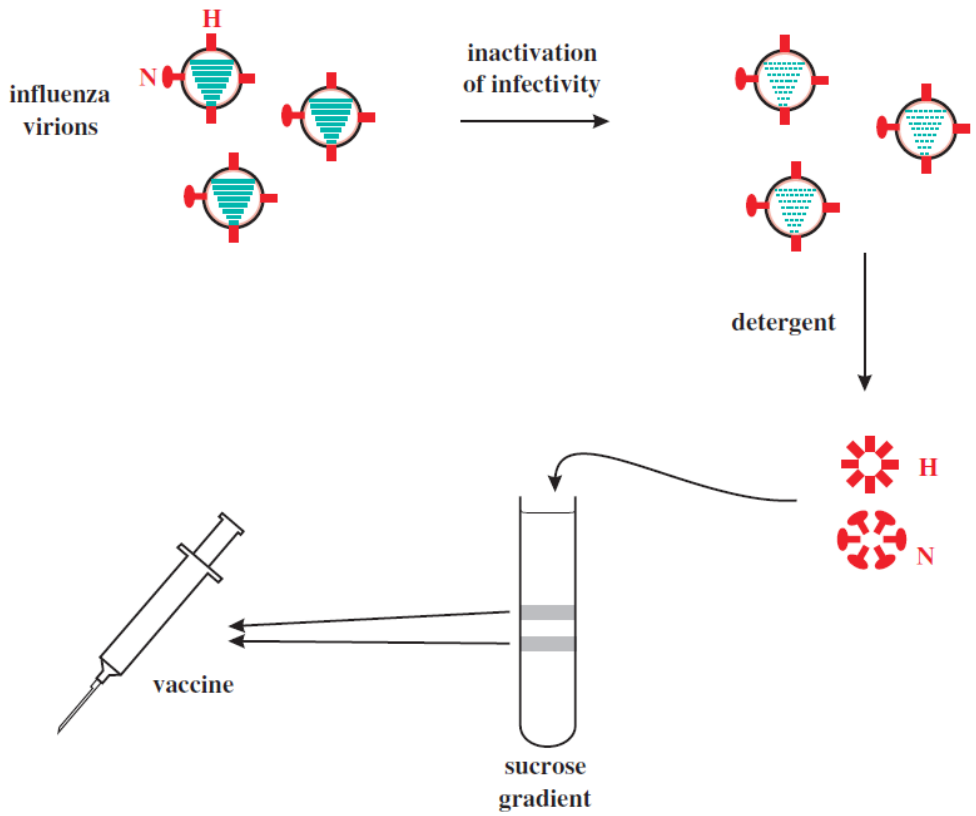


Figure 25.3 **Outline of production method for influenza virus subunit vaccine.** Hemagglutinin (H) and neuraminidase (N) are extracted from inactivated influenza virions and purified by sucrose gradient centrifugation. The bands from the gradient are harvested and incorporated into the vaccine.

Figure 25.4 Production of vaccine in chick embryos.
Source: Courtesy of the World Health Organization.

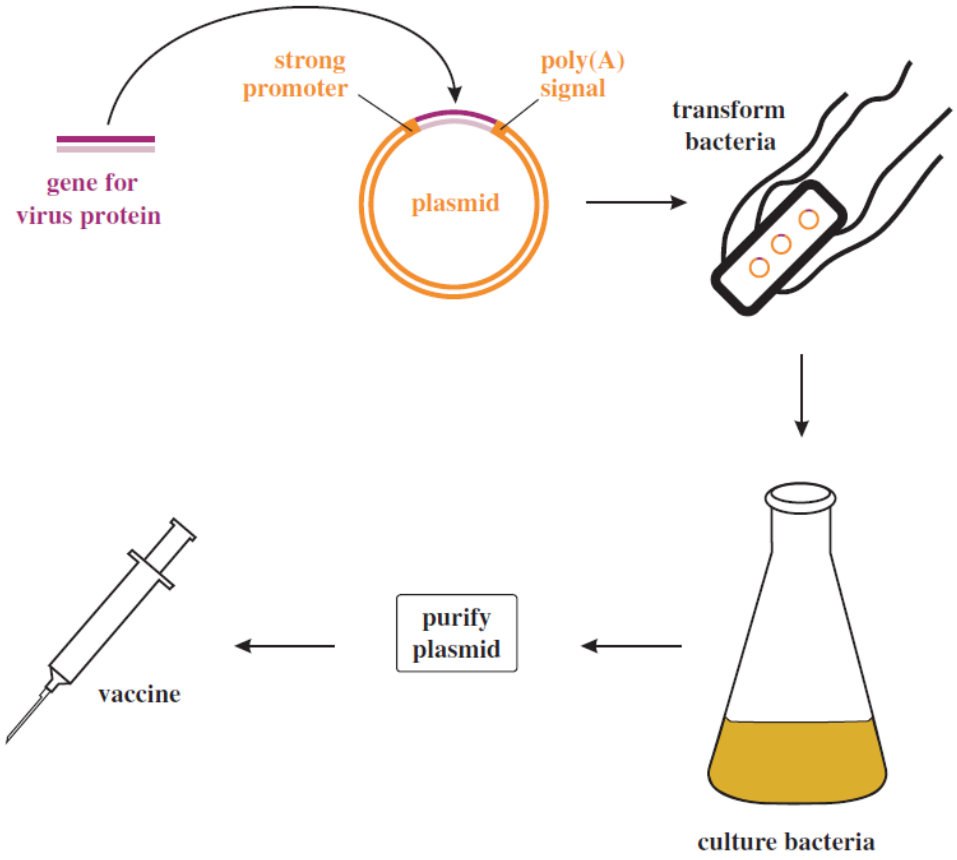
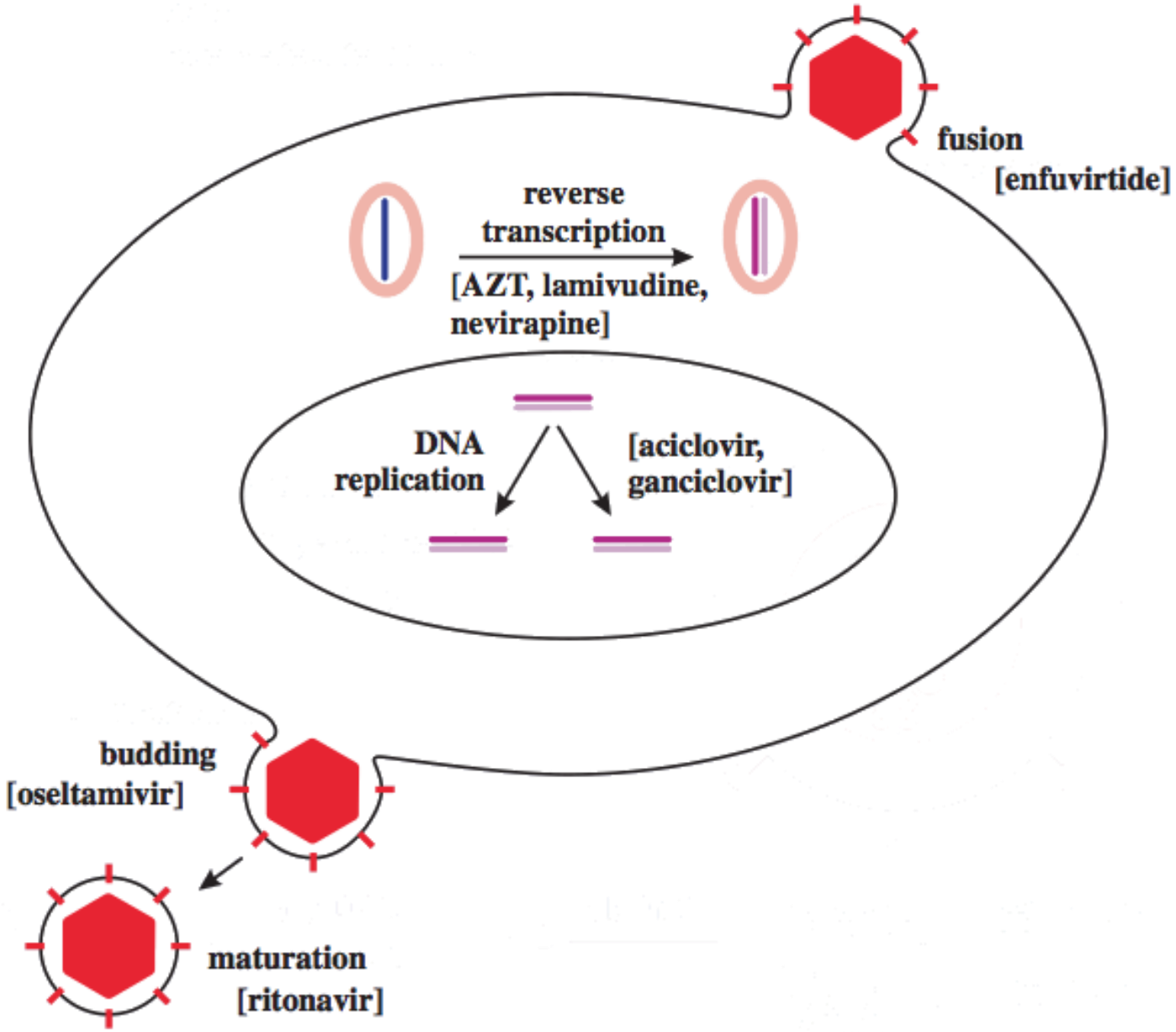


Figure 25.5 **Production of a DNA vaccine.** The virus protein gene is inserted into a plasmid, which is then cloned in bacteria. The plasmid is extracted from the bacterial cells, purified, and incorporated into a vaccine.

Learning outcomes

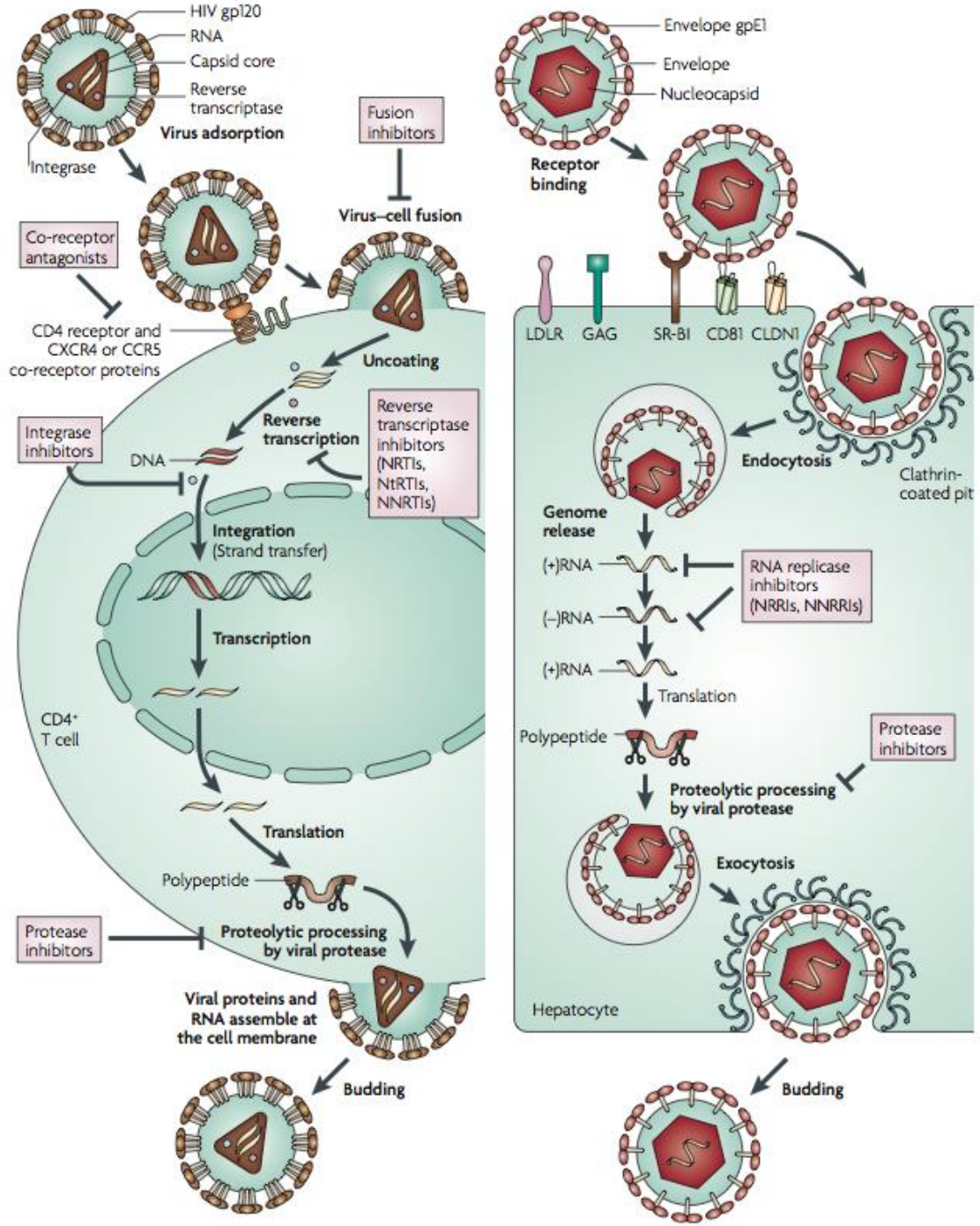
- explain how virus diseases are controlled with vaccines
- evaluate the types of virus vaccine in medical and veterinary use
- evaluate types of virus vaccine that are experi-mental
- describe methods used to manufacture virus vaccines
- evaluate procedures designed to ensure the safety of virus vaccines

Antiviral compounds



HIV

HCV


HIV gp120
RNA
Capsid core
Reverse transcriptase
Integrase
Virus adsorption
Fusion inhibitors
Virus–cell fusion
Co-receptor antagonists
CD4 receptor and CXCR4 or CCR5 co-receptor proteins
Uncoating
Reverse transcription
Reverse transcriptase inhibitors (NRTIs, NtRTIs, NNRTIs)
Integrase inhibitors
DNA
Integration (Strand transfer)
Transcription
CD4+ T cell
Translation
Polypeptide
Protease inhibitors
Proteolytic processing by viral protease
Viral proteins and RNA assemble at the cell membrane
Budding
Envelope gpE1
Envelope
Nucleocapsid
Receptor binding
LDLR
GAG
SR-BI
CD81
CLDN1
Endocytosis
Clathrin-coated pit
Genome release
(+)RNA
(–)RNA
(+)RNA
RNA replicase inhibitors (NRRIs, NNRRIs)
Translation
Polypeptide
Protease inhibitors
Proteolytic processing by viral protease
Exocytosis
Hepatocyte
Budding

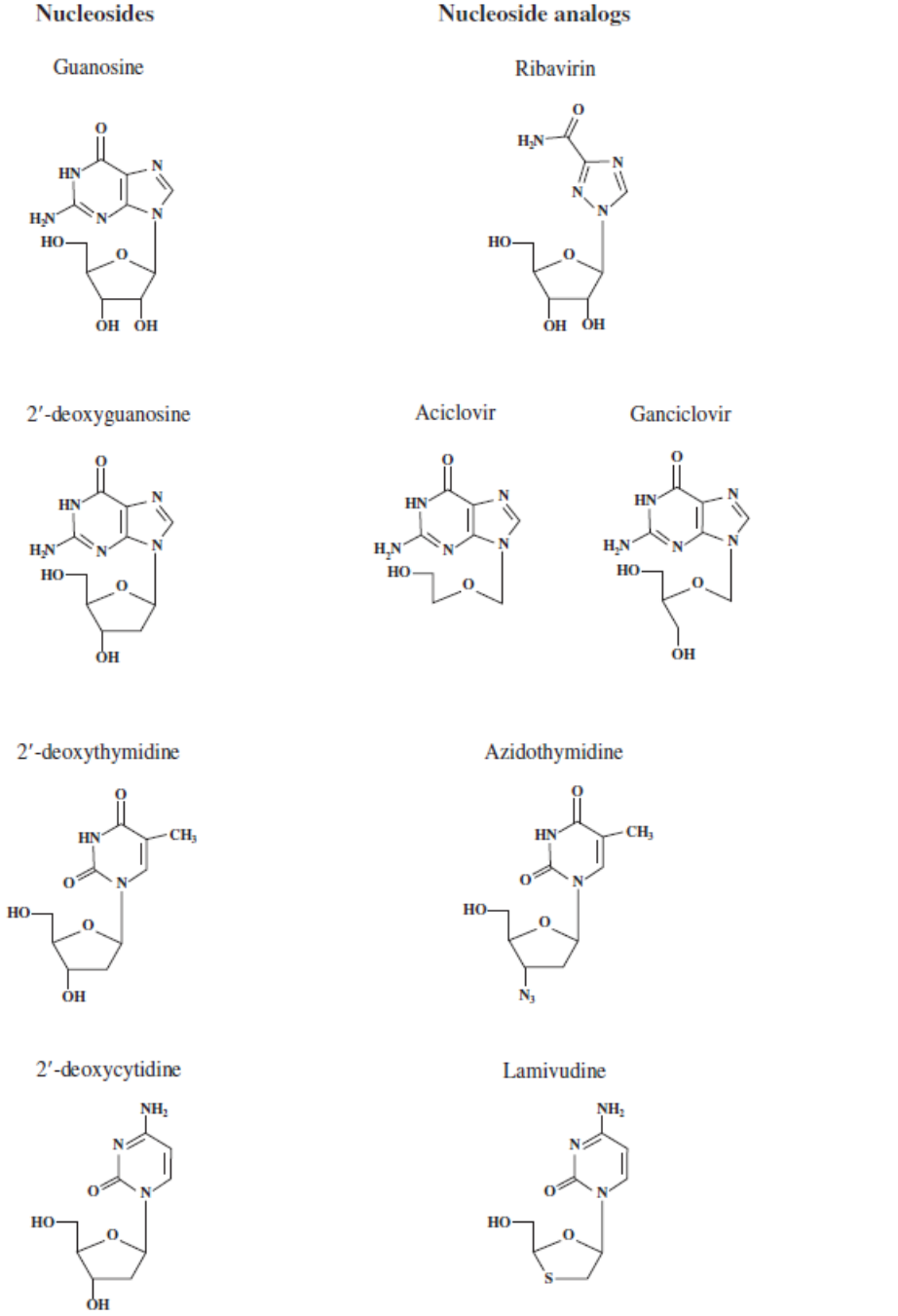


Figure 26.2 **Nucleoside analogs used as anti-viral drugs.** The analogs are derived from the nucleosides shown on the left.

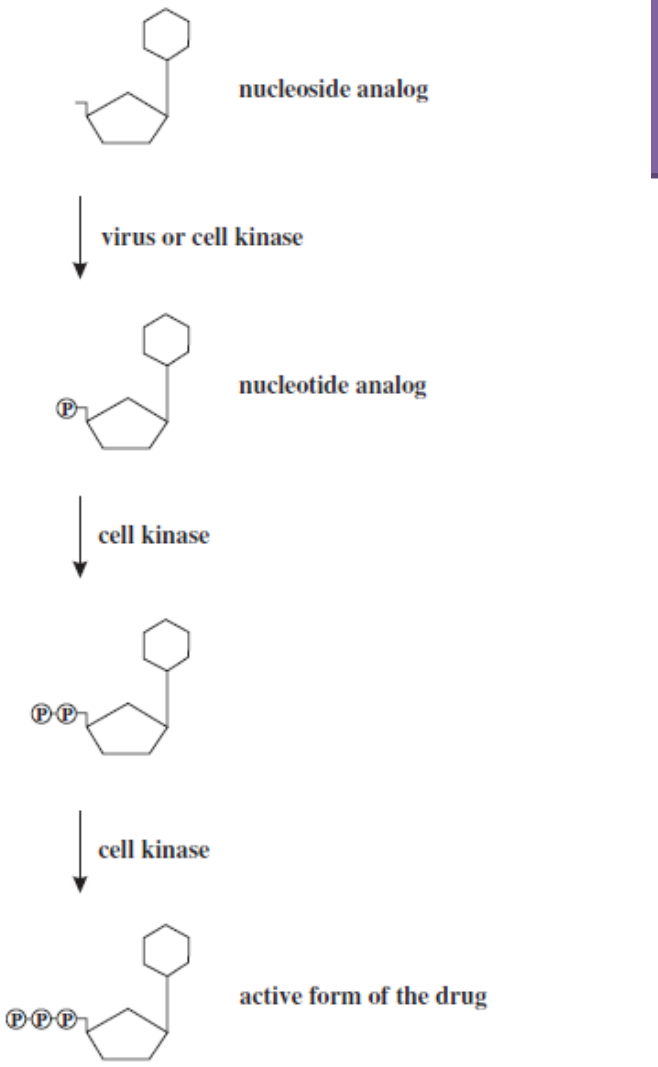
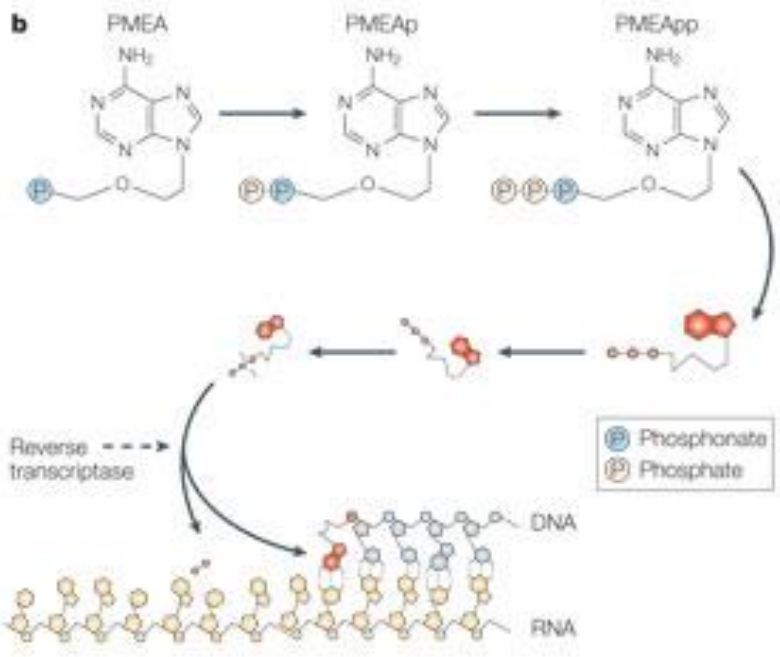
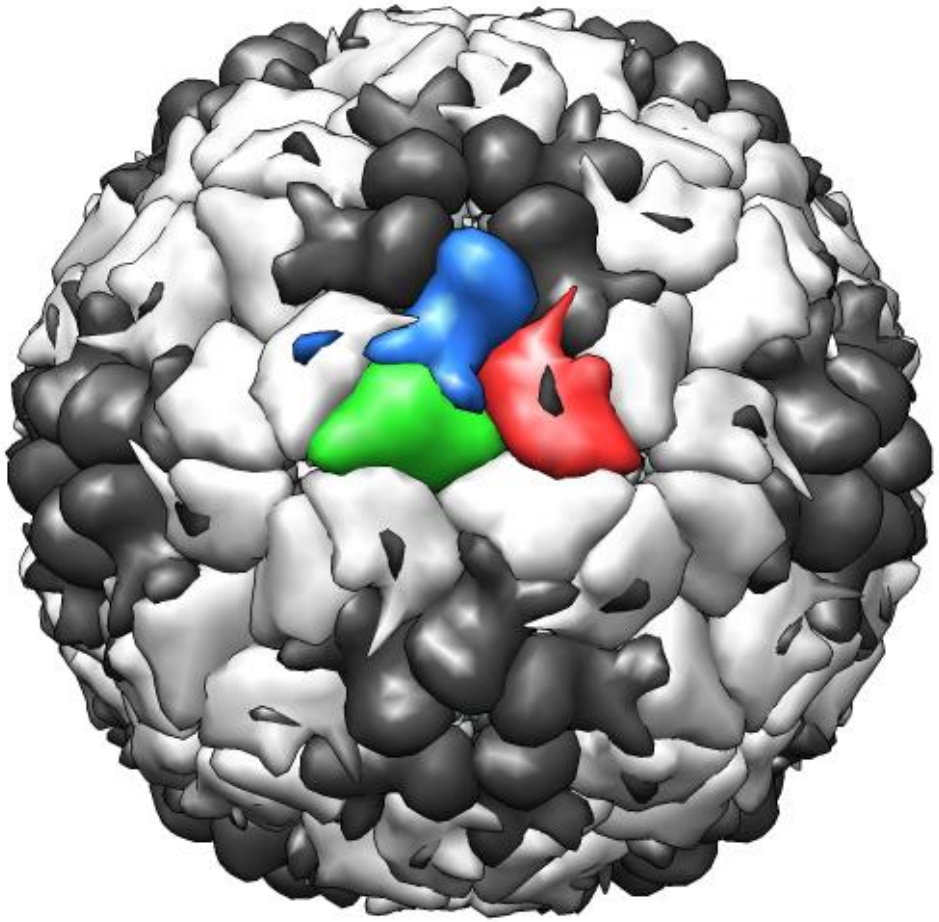
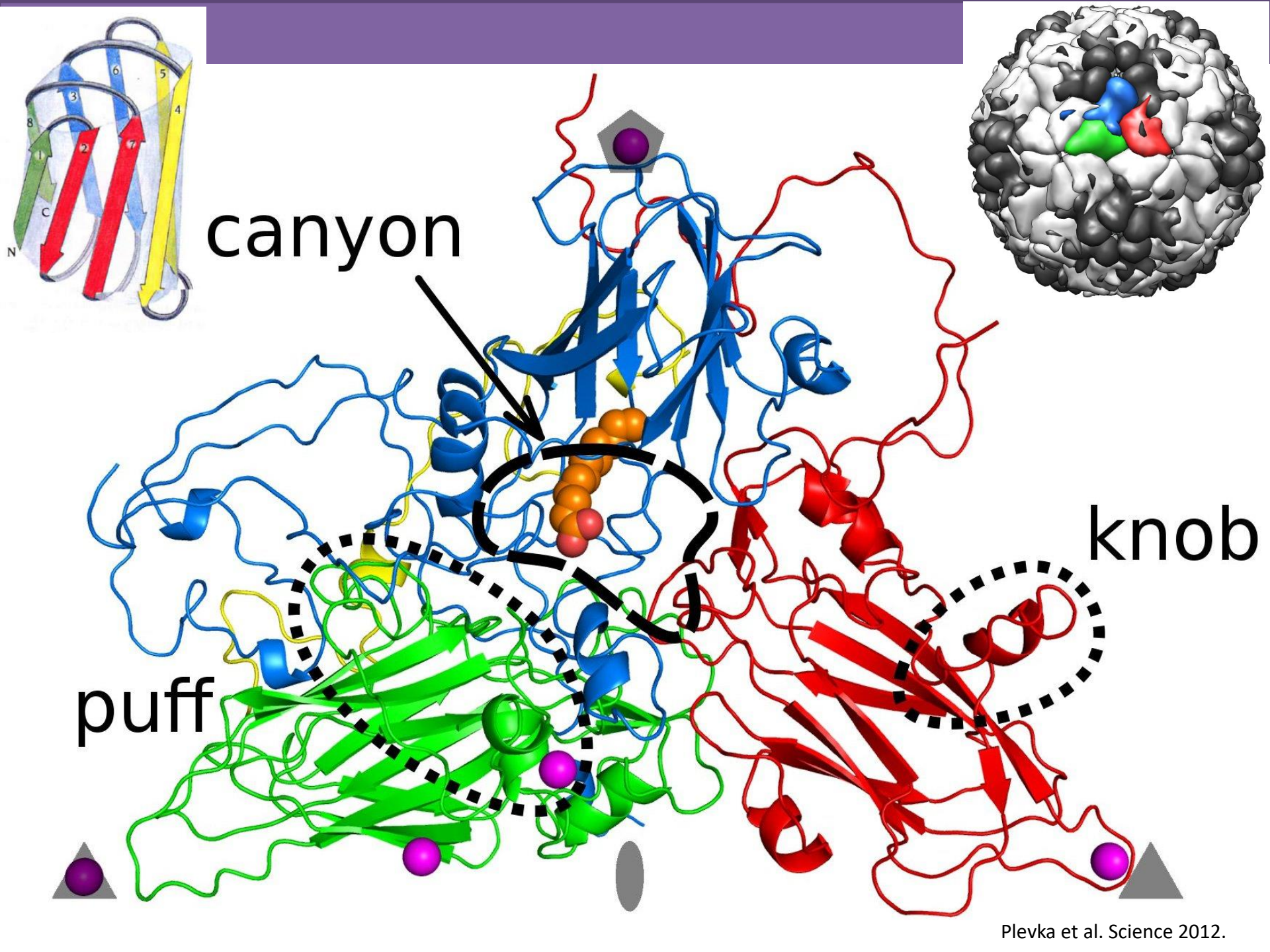


Figure 26.3 **Phosphorylation of a nucleoside analog.** The active form of the drug is the 5′ triphosphate derivative of the nucleoside analog.



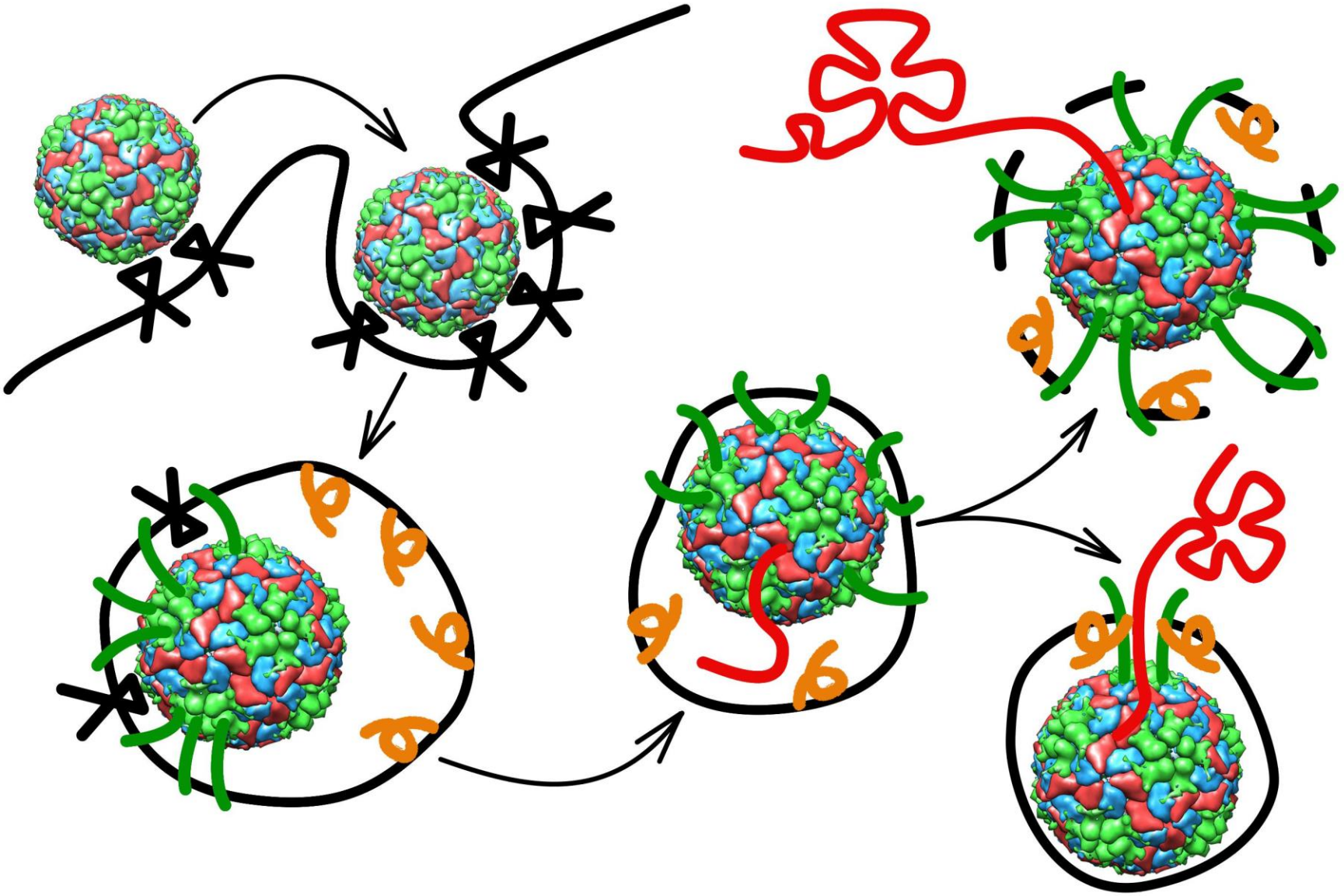
Picornavirus virion

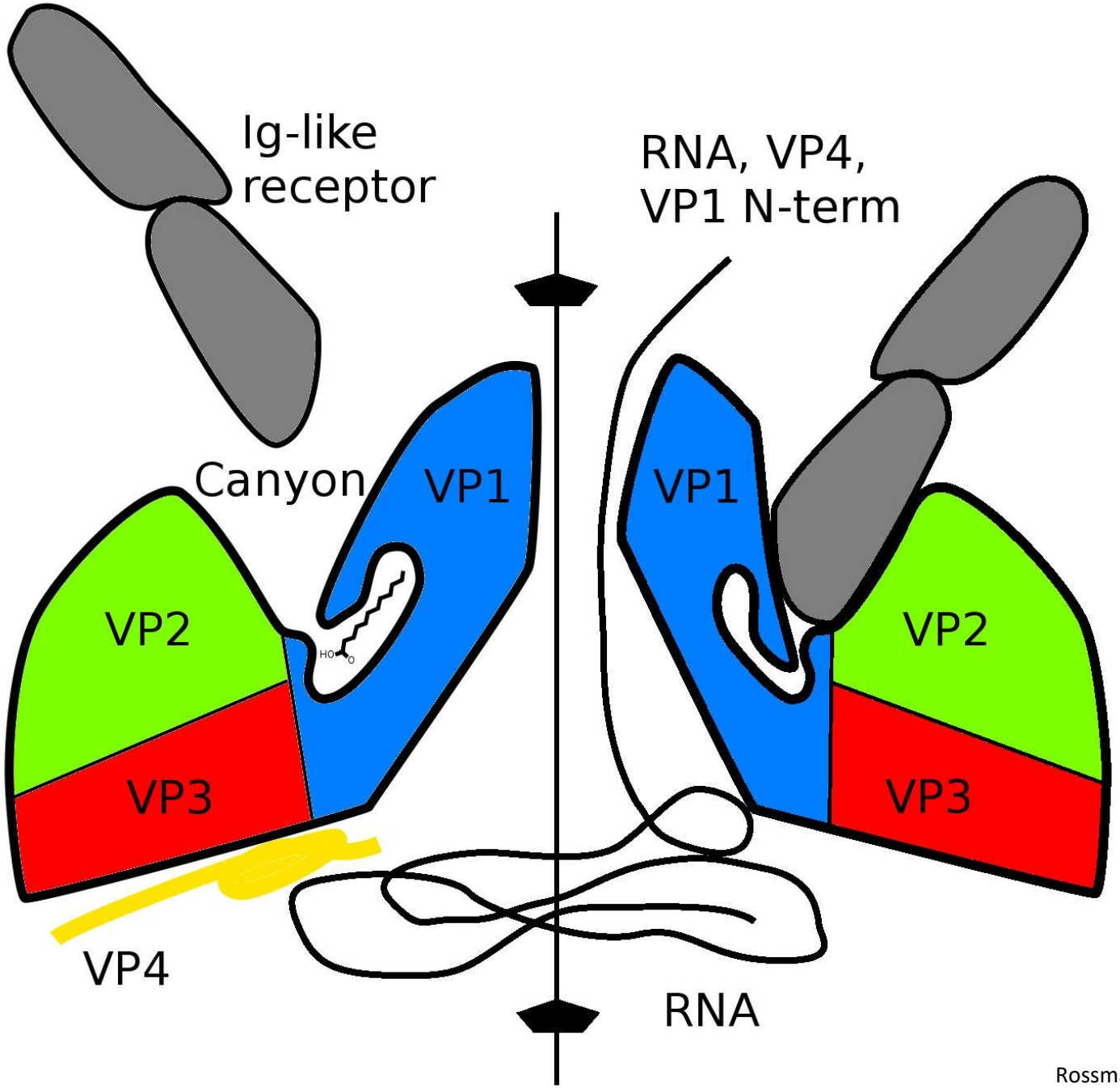




Plevka et al. Science 2012.

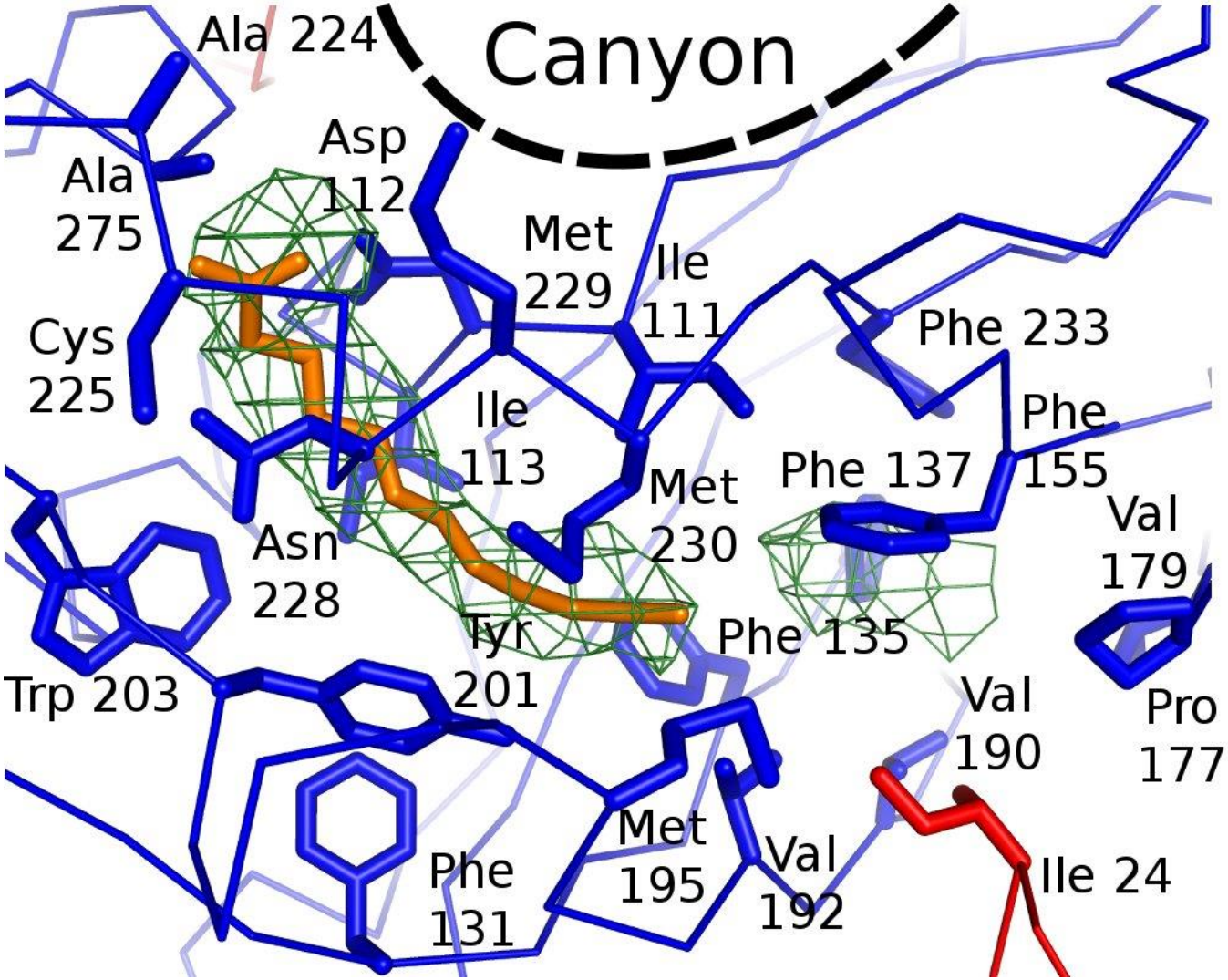
1. Genome delivery into cytoplasm

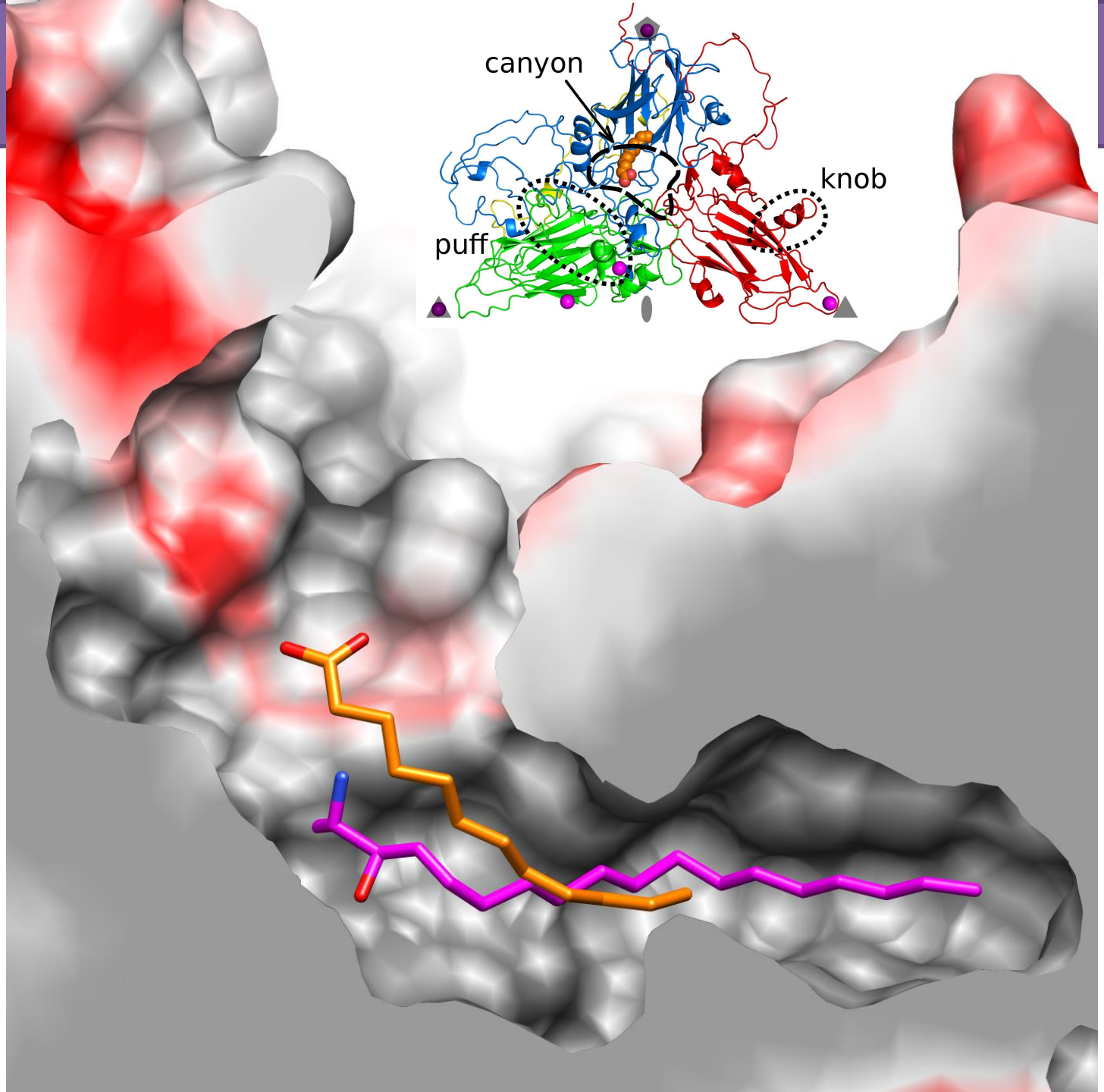


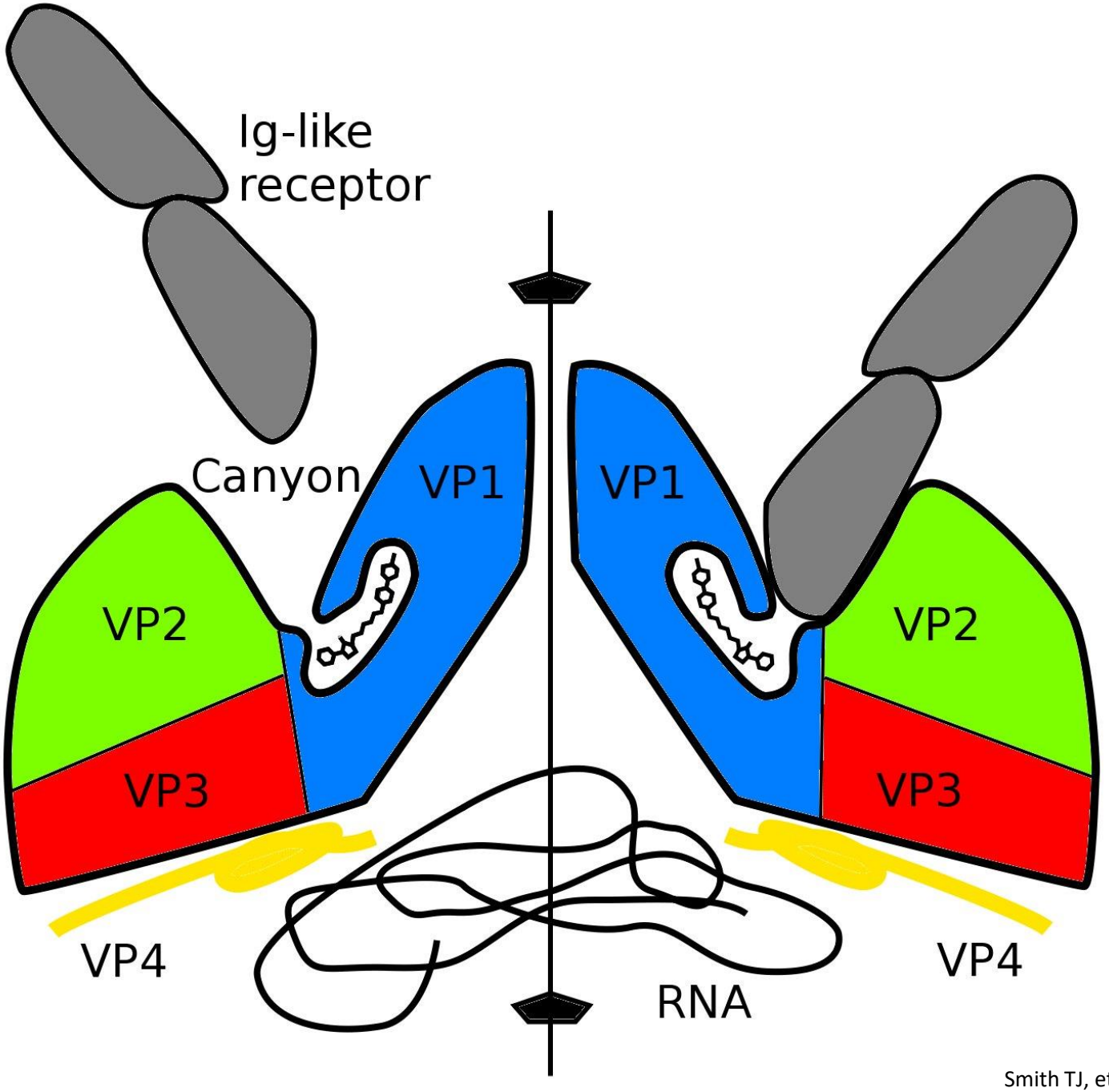


Rossmann Prot Sci, 1994

Pocket factor in EV71

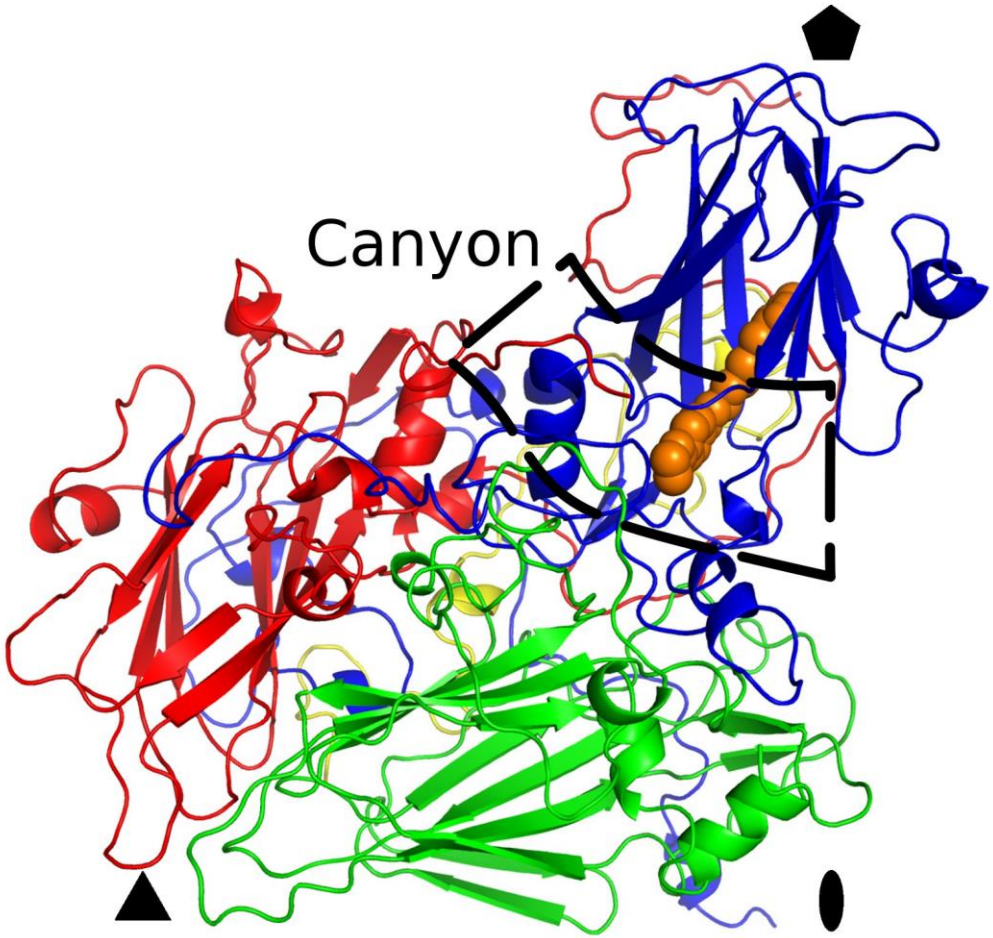


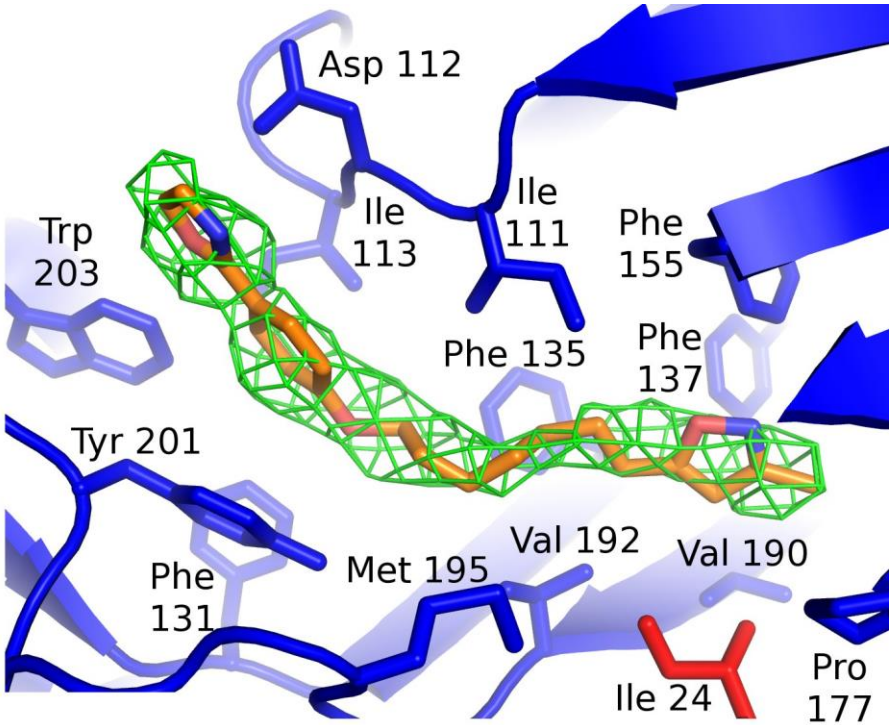

canyon
knob
puff



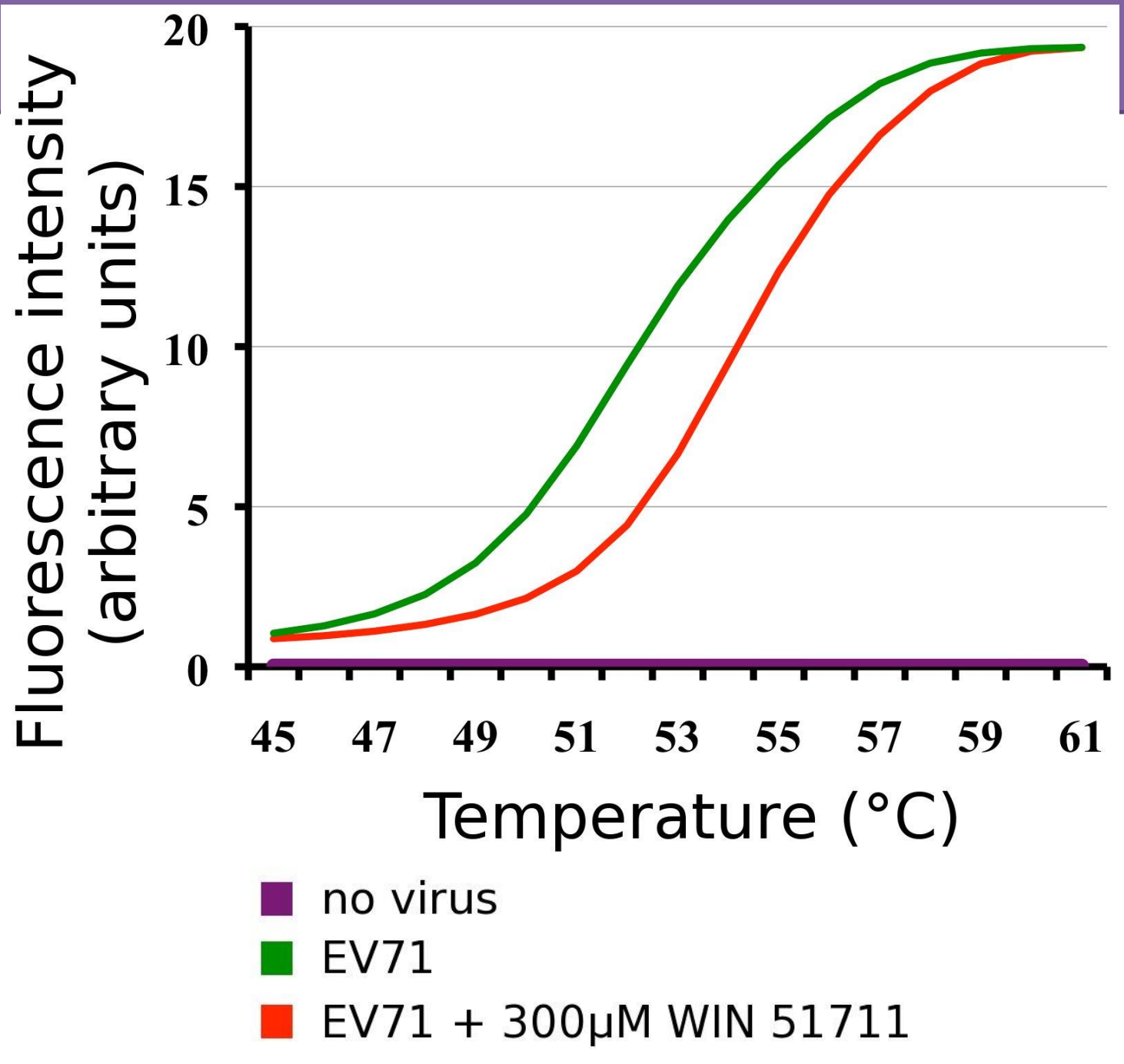
Smith TJ, et al. Science, 1986

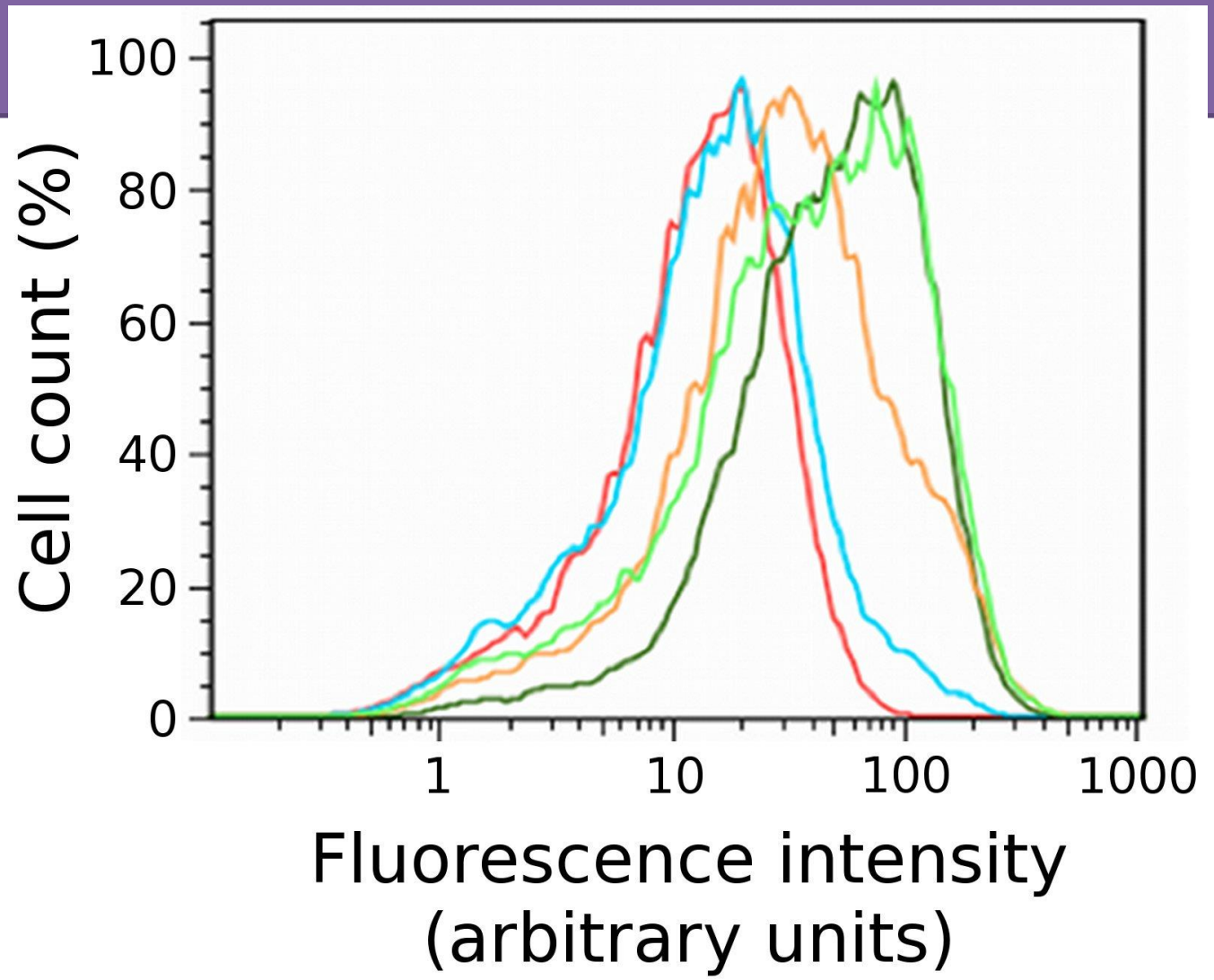
Inhibition of EV71 by WIN 51711





Plevka et al. PNAS 2013


Fluorescence intensity
(arbitrary units)
20
15
10
5
0
45
47
49
51
53
55
57
59
61
Temperature (°C)
no virus
EV71
EV71 + 300μM WIN 51711


Cell count (%)
100
80
60
40
20
0
1
10
100
1000
Fluorescence intensity
(arbitrary units)
no virus
EV71
EV71 + 146μM WIN 51711
EV71 + 291μM WIN 51711
EV71 + 583μM WIN 51711

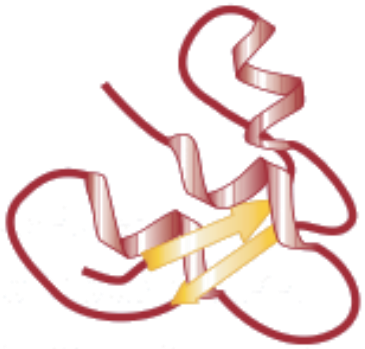
Learning outcomes

- evaluate procedures used to develop new anti-viral drugs
- describe the modes of action of selected anti-viral drugs
- discuss virus resistance to drugs

Prions

PRION (INfectious PROtein)

Normal protein



More α helix than β sheet

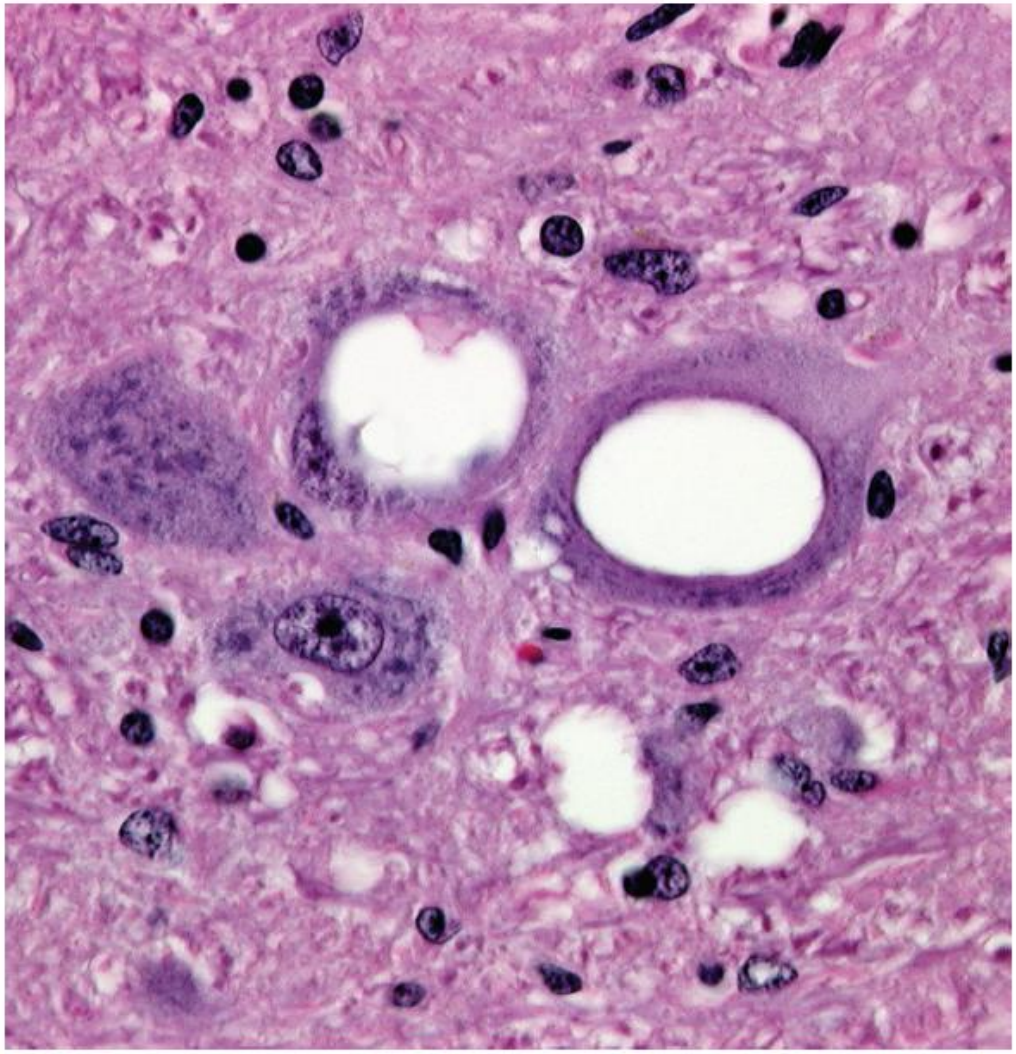
Misfolded protein

Mainly β sheet

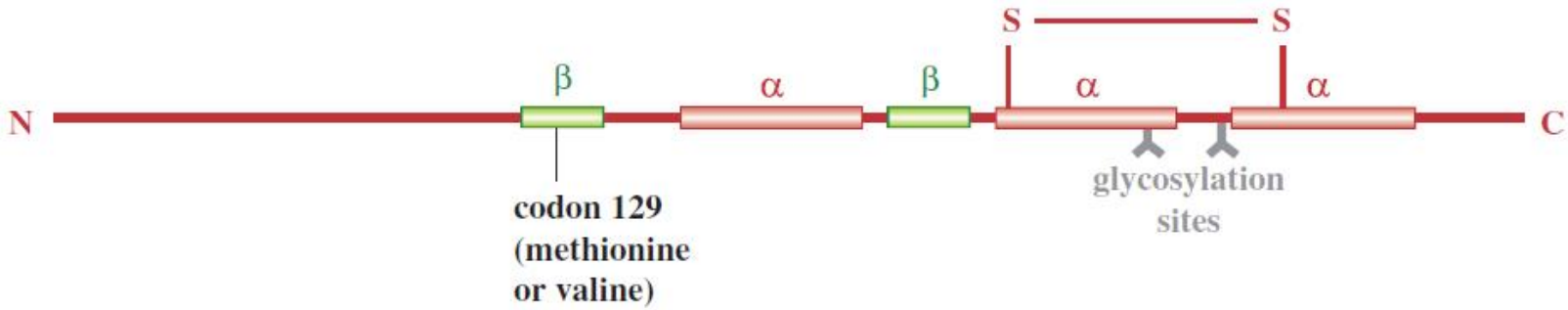
Prion diseases:

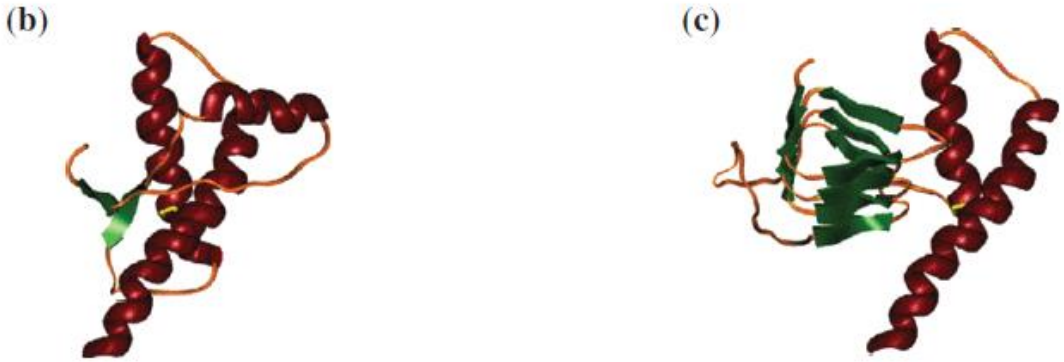
- scrapie (sheep)
- bovine spongiform encephalopathy
- sporadic Creutzfeldt-Jakob disease (humans)
- variant Creutzfeldt-Jakob disease (humans)

Brain with Scrapie



Normal and misfolded form of prion





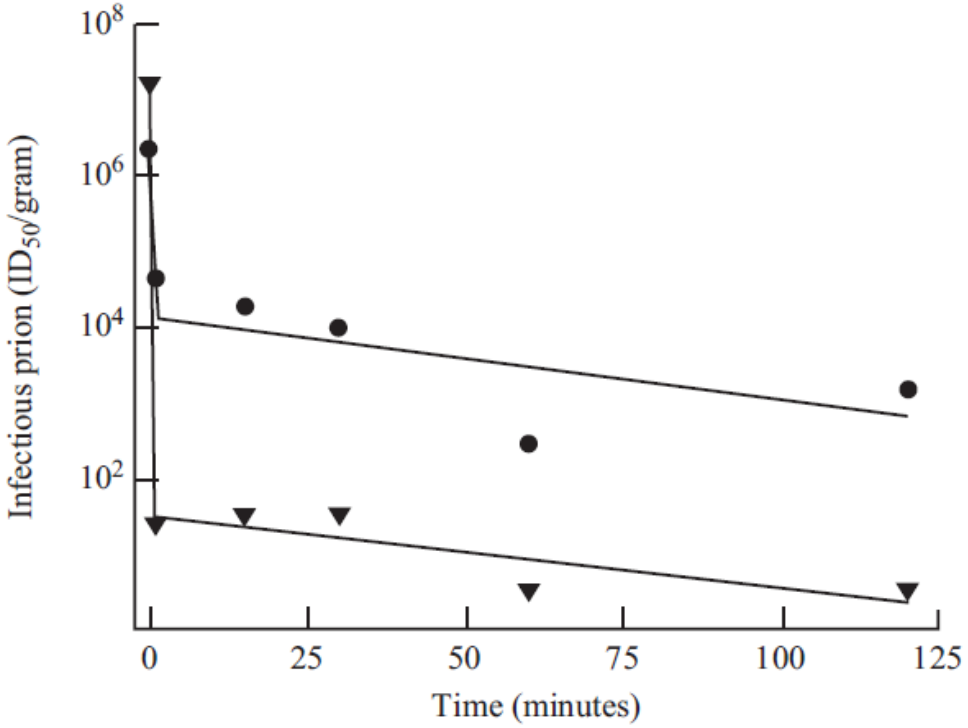


Figure 27.3 Inactivation of two strains of scrapie prion in an autoclave at 126 °C.

Source: Data from Somerville (2002) *Trends In Biochemical Sciences*, 27, 606. Reprinted by permission of Elsevier and the author.

Creutzfeldt-Jacob disease x BSE

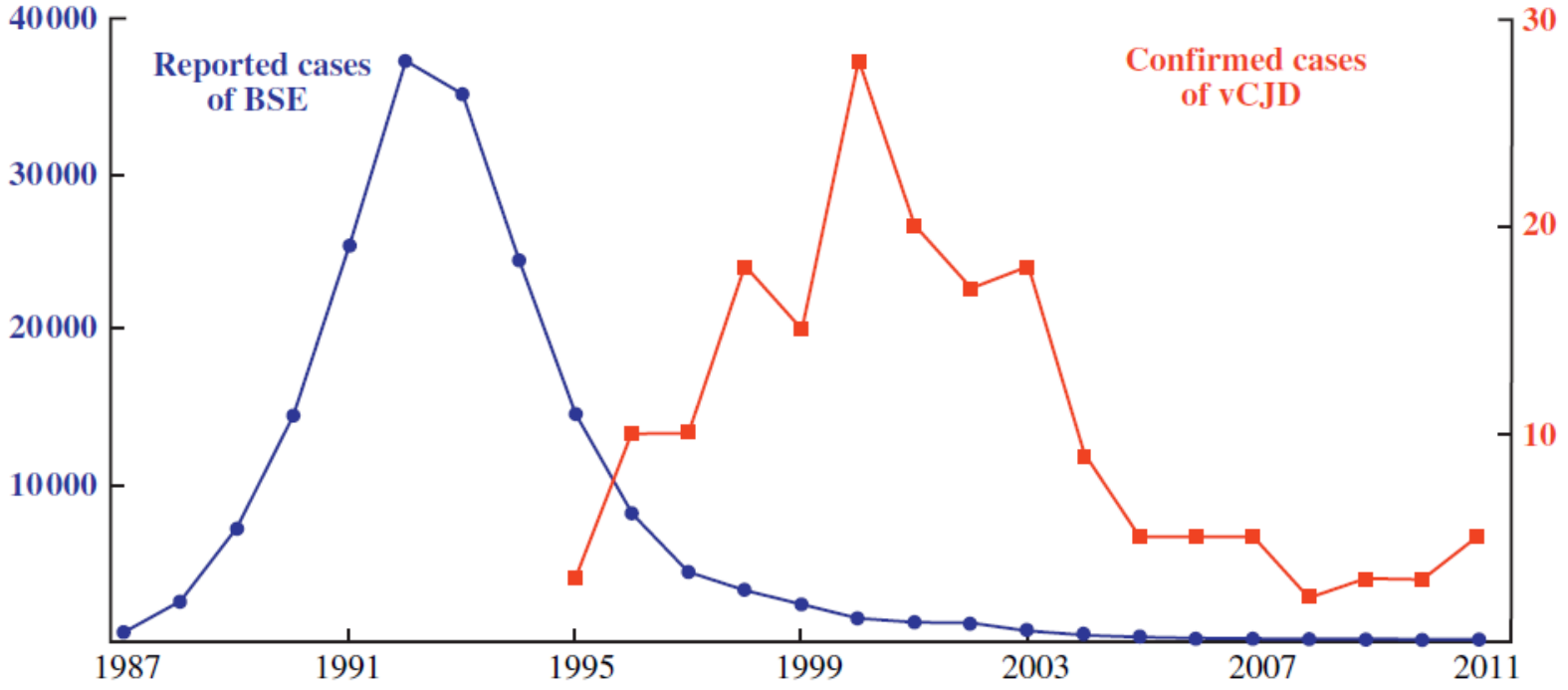
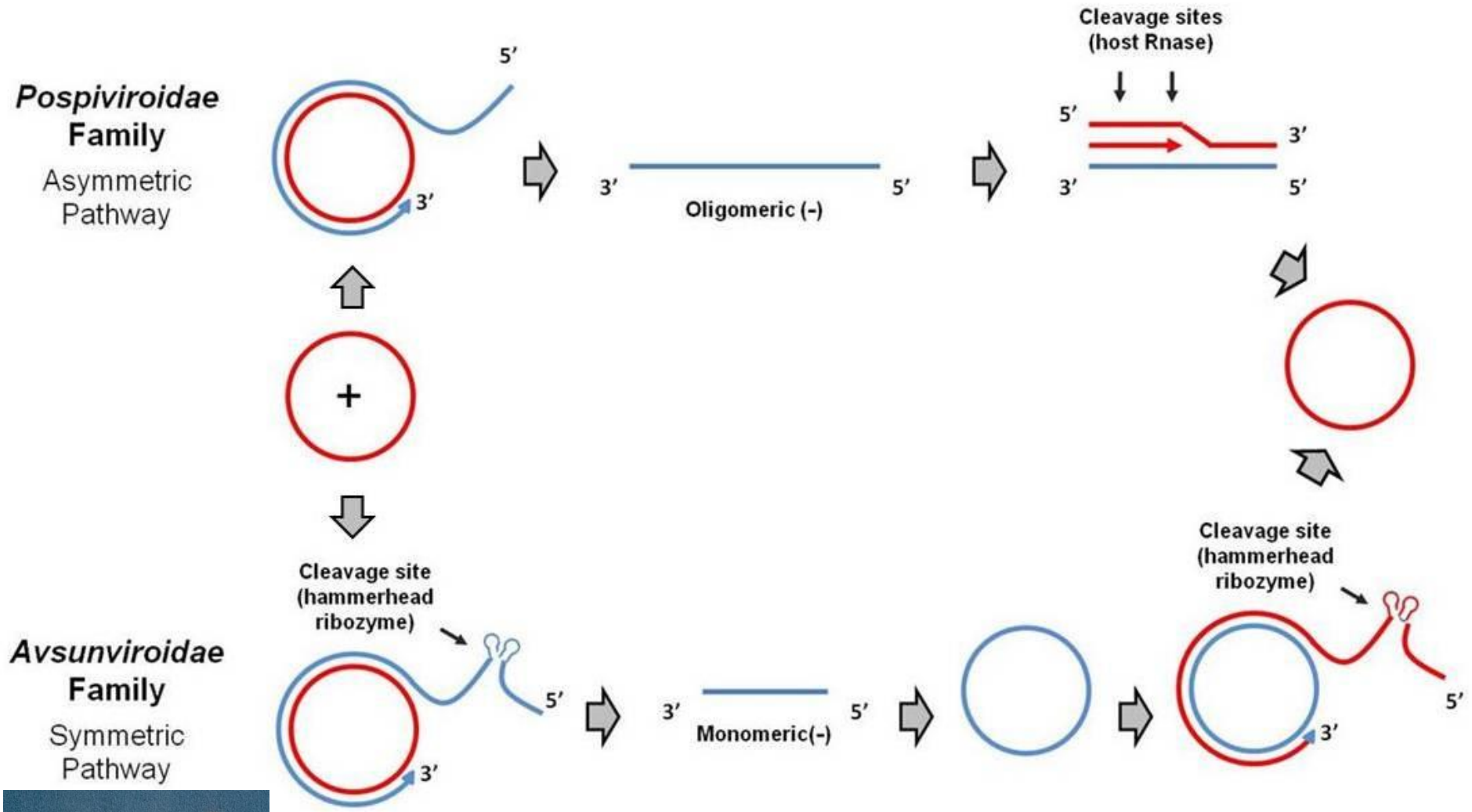


Figure 27.4 Numbers of cases of BSE and vCJD in the UK.

Source: BSE data from World Organization for Animal Health. vCJD data from UK National CJD Surveillance Unit.

Viroids



Virophage - Sputnik