Introduction to Virology

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Contents of Teaching in Medical Virology Lecture:

Introduction

- **Viruses contribute significantly to the global burden of infectious disease.**
- We experience countless infections throughout their lives, with particularly high frequency in **early childhood.** While most of these are mild, viruses may cause severe disease in susceptible individuals, such as the mal-nourished, immuno-compromised, the very old and the very young**.**
- Recent years have also seen the **emergence of new viral diseases** such as HIV, SARS and "swine flu" (H1N1 pandemic influenza A).

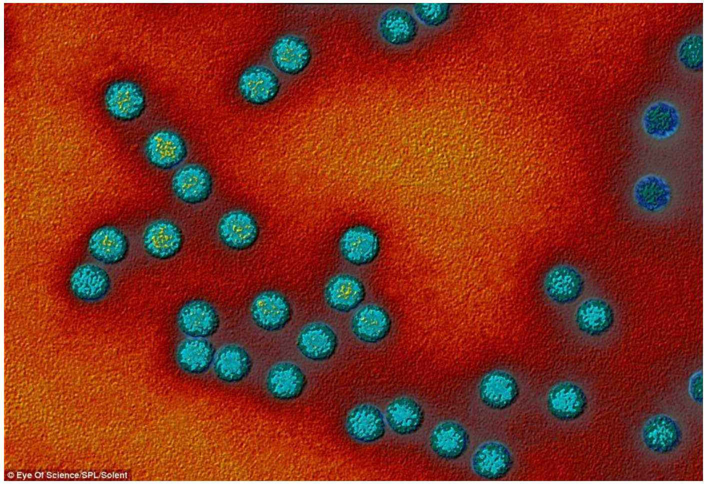
What is a virus?

Viruses are uniquely different from the many uni-cellular micro-organisms you have studied so far. **Protozoa, yeasts, bacteria, mycoplasmas, rikettsiae and chlamydiae** are all living organisms with the following features in common:

- They are all **cells**
- They store their **genetic information** as **DNA**
- Within their cell, they contain all the **organelles** necessary for producing energy and **synthesizing proteins, carbohydrates**, cell wall structures etc.
- Replicate by means of **binary fission**

What is a virus?

- **Viruses do not share these properties**. They are **not cells**. They are very simple structures consisting essentially of a **nucleic acid genome**, protected by a shell of **protein**. They are metabolically inert and can only replicate once they are inside a host cell.



Polio virus; ssRNA genome

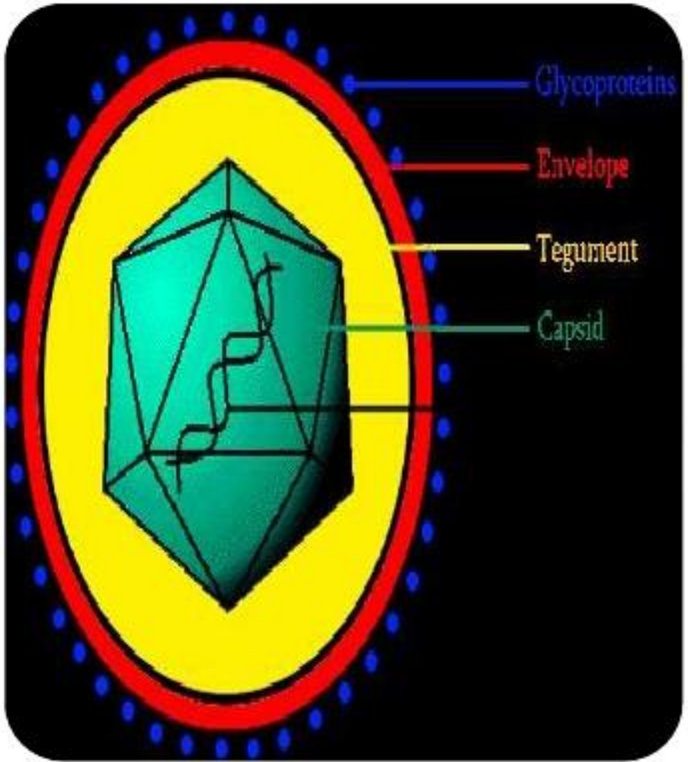
- The **genome** consists of only one type of nucleic acid: **either RNA or DNA**.
- Most DNA viruses are **double stranded (ds)** and most RNA viruses have a **single stranded (ss)** genome.
- A ssRNA genome may be either positive sense (this means that it can be used as mRNA to make proteins) or negative sense. Negative sense RNA is complimentary to mRNA, in other words, it has to be copied into mRNA. The viral genome codes only for the few proteins necessary for replication: some proteins are **non-structural** e.g. polymerase and some are **structural**, i.e. they form part of the virion structure.

Terminology

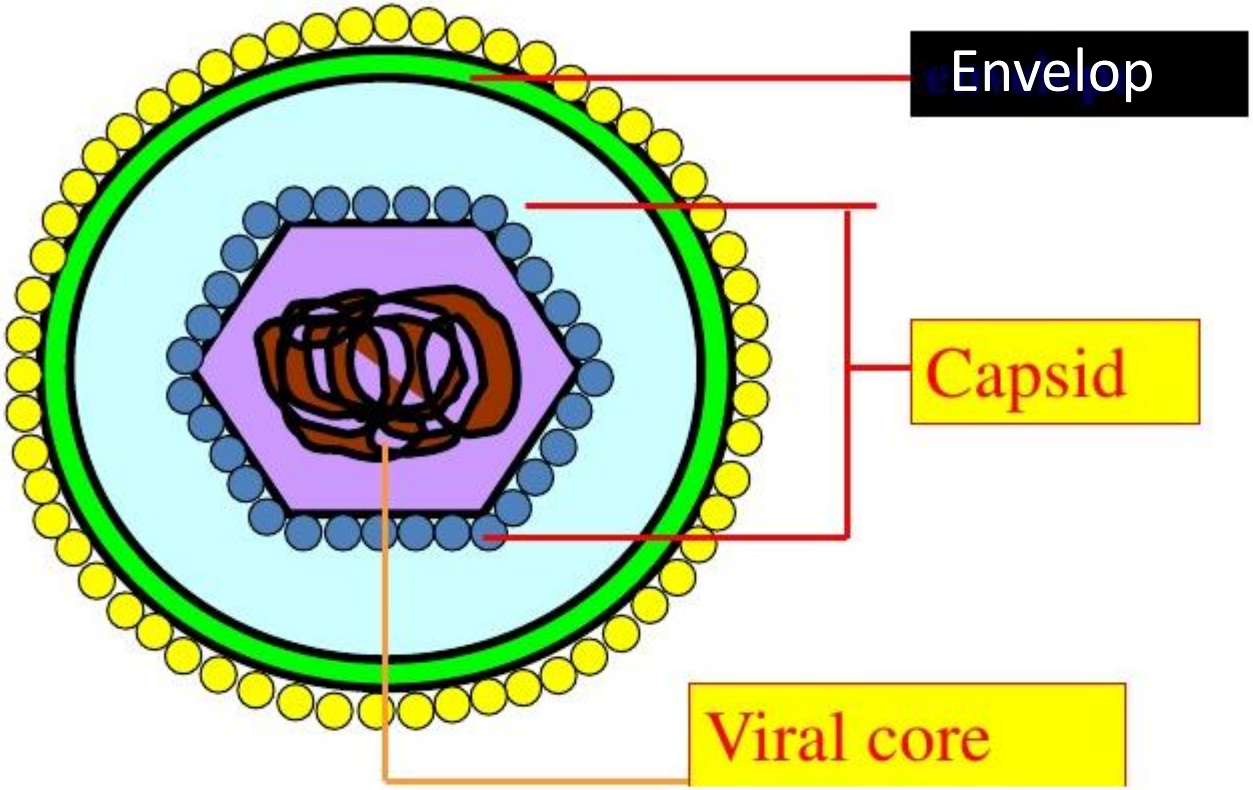
- **Virion** = virus particle
- **Capsid = protein shell** which surrounds and protects the genome. It is built up of multiple (identical) protein sub-units called **capsomers.** Capsids are either **icosahedral** or **tubular** in shape
- **Nucleocapsid** = genome plus capsid
- **Envelope =** lipid membrane which surrounds some viruses. It is derived from the plasma membrane of the host cell.
- **Peplomers =** proteins found in the envelope of the virion. They are usually glycosylated and are thus more commonly known as **glycoproteins.**

Virion

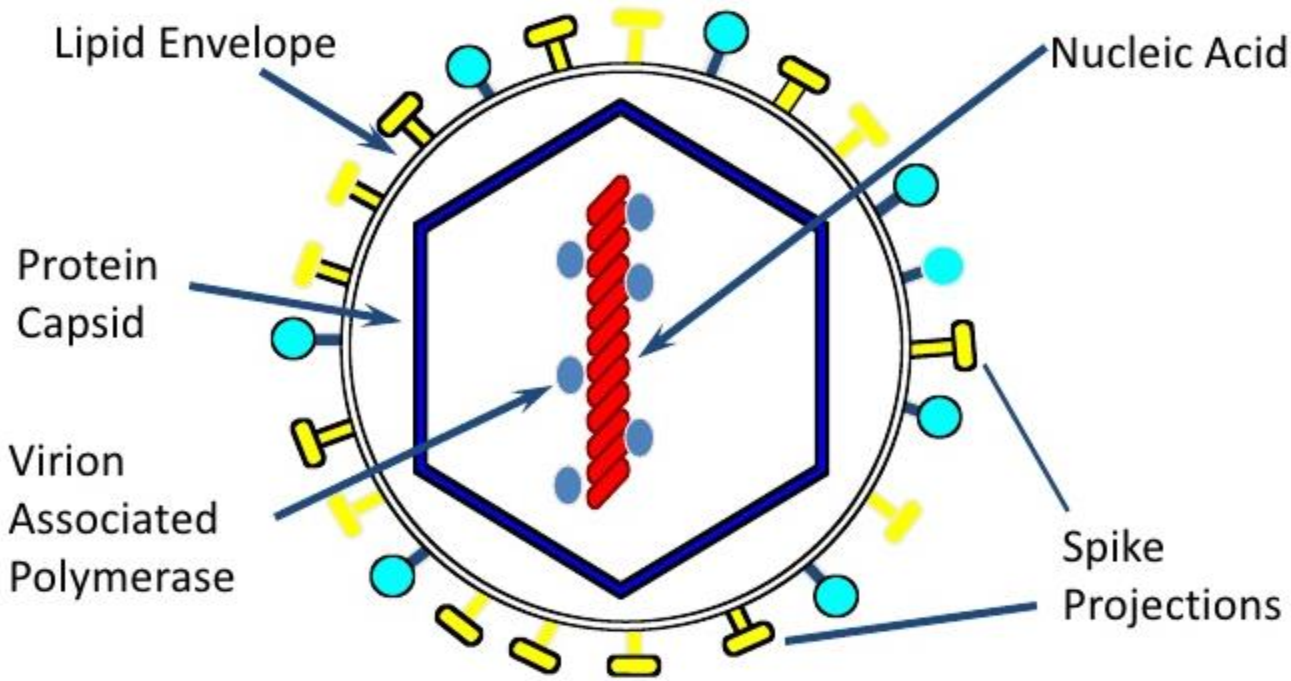
- **The complete infectious unit of virus particle**
- **Structurally mature, extracellular virus particles.**



Virion

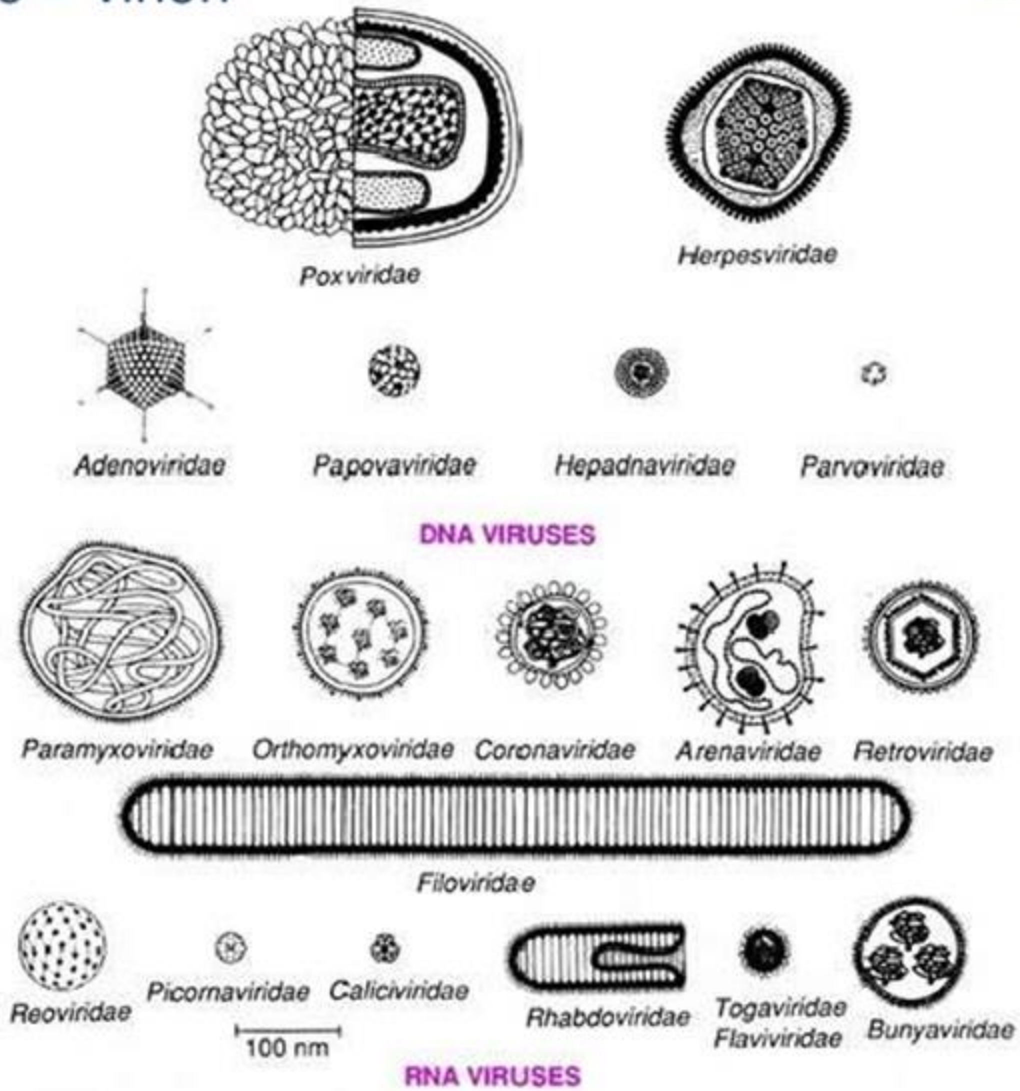


Virion Structure



Virus particle = virion

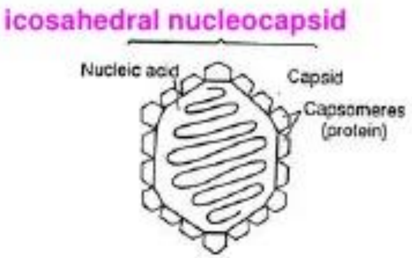
White DO and Fenner, FJ.
al Virology, 4th Ed. 1994



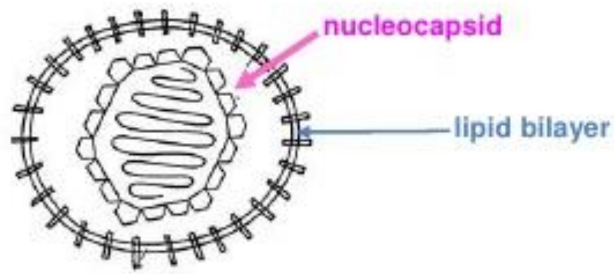
How are viruses named?

- Based on:
  - the disease they cause
    poliovirus, rabies virus
  - the type of disease
    murine leukemia virus
  - geographic locations
    Sendai virus, Coxsackie virus
  - their discovers
    Epstein-Barr virus
  - how they were originally thought to be contracted
    dengue virus (“evil spirit”), influenza virus (the “influence” of bad air)
  - combinations of the above
    Rous Sarcoma virus

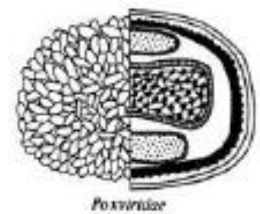
5 BASIC TYPES OF VIRAL STRUCTURE



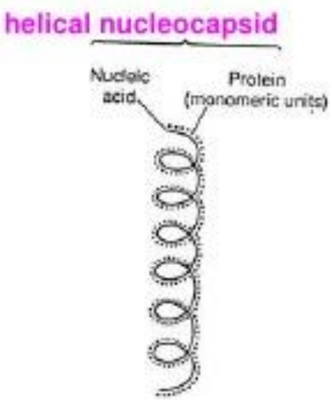
ICOSAHEDRAL



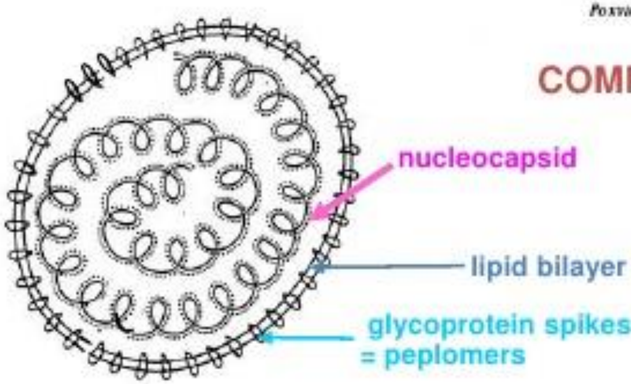
ENVELOPED ICOSAHEDRAL



COMPLEX



HELICAL



ENVELOPED HELICAL

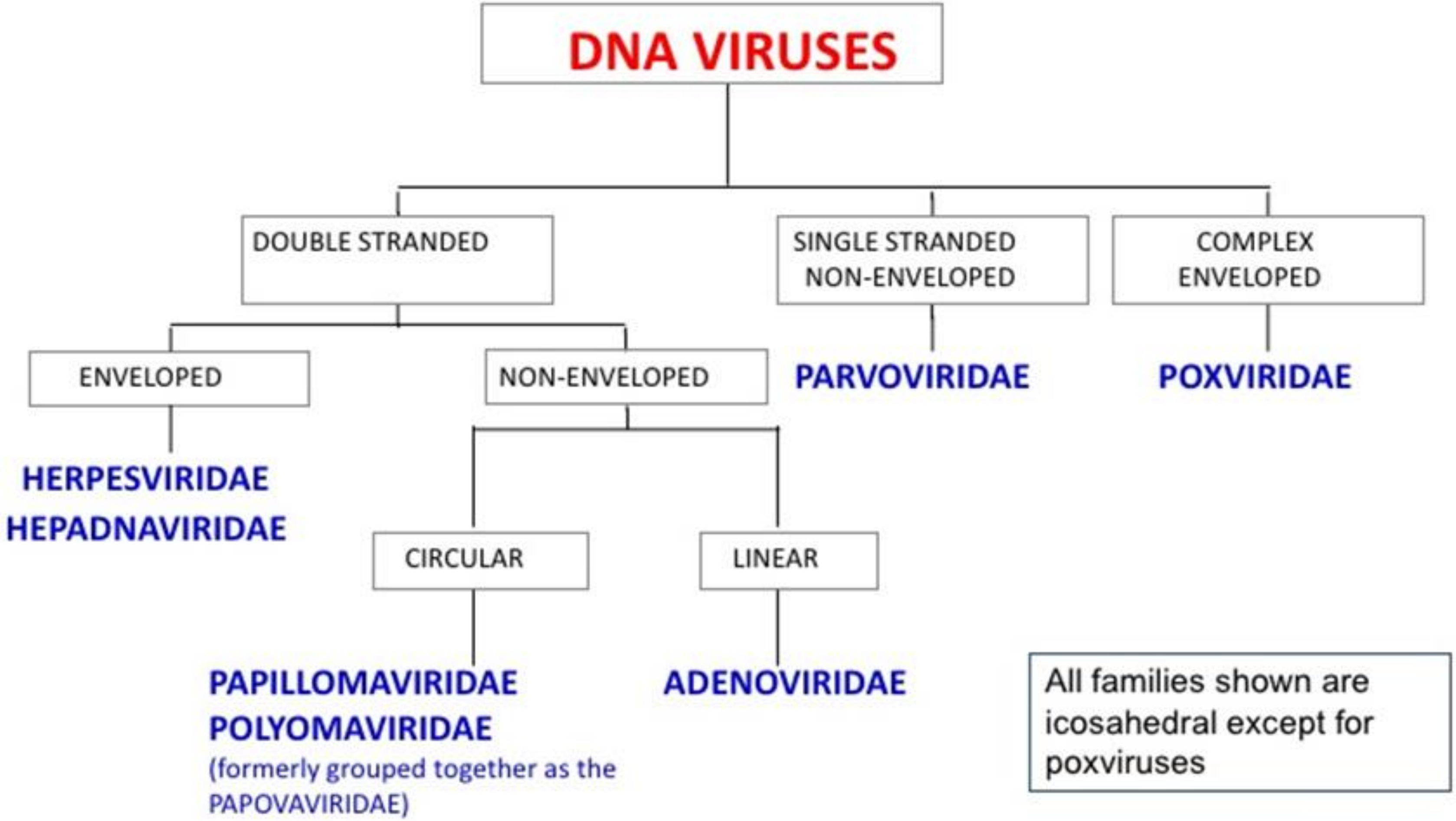
Adapted from Schaechter et al., Mechanisms of Microbial Disease

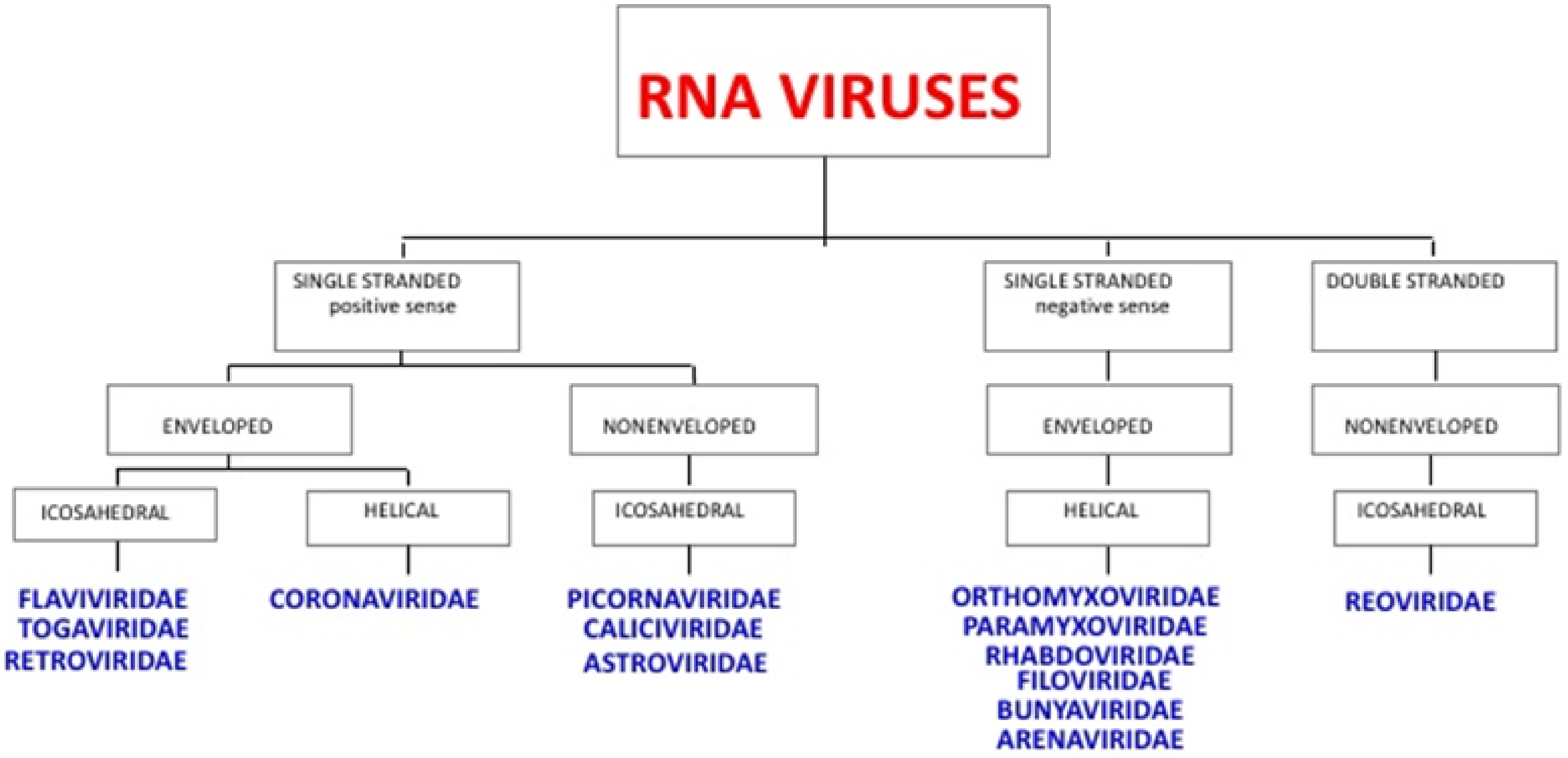
The Baltimore classification system

Based on genetic contents and replication strategies of viruses. According to the Baltimore classification, viruses are divided into the following seven classes:

1. dsDNA viruses
2. ssDNA viruses
3. dsRNA viruses
4. (+) sense ssRNA viruses (codes directly for protein)
5. (-) sense ssRNA viruses
6. RNA reverse transcribing viruses
7. DNA reverse transcribing viruses

where "ds" represents "double strand" and "ss" denotes "single strand".


DNA VIRUSES
DOUBLE STRANDED
SINGLE STRANDED NON-ENVELOPED
COMPLEX ENVELOPED
ENVELOPED
NON-ENVELOPED
PARVOVIRIDAE
POXVIRIDAE
HERPESVIRIDAE
HEPADNAVIRIDAE
CIRCULAR
LINEAR
PAPILLOMAVIRIDAE
POLYOMAVIRIDAE
(formerly grouped together as the PAPOVAVIRIDAE)
ADENOVIRIDAE
All families shown are icosahedral except for poxviruses


RNA VIRUSES
SINGLE STRANDED positive sense
SINGLE STRANDED negative sense
DOUBLE STRANDED
ENVELOPED
NONENVELOPED
ENVELOPED
NONENVELOPED
ICOSAHEDRAL
HELICAL
ICOSAHEDRAL
HELICAL
ICOSAHEDRAL
FLAVIVIRIDAE
TOGAVIRIDAE
RETROVIRIDAE
CORONAVIRIDAE
PICORNAVIRIDAE
CALICIVIRIDAE
ASTROVIRIDAE
ORTHOMYXOVIRIDAE
PARAMYXOVIRIDAE
RHABDOVIRIDAE
FILOVIRIDAE
BUNYAVIRIDAE
ARENAVIRIDAE
REOVIRIDAE

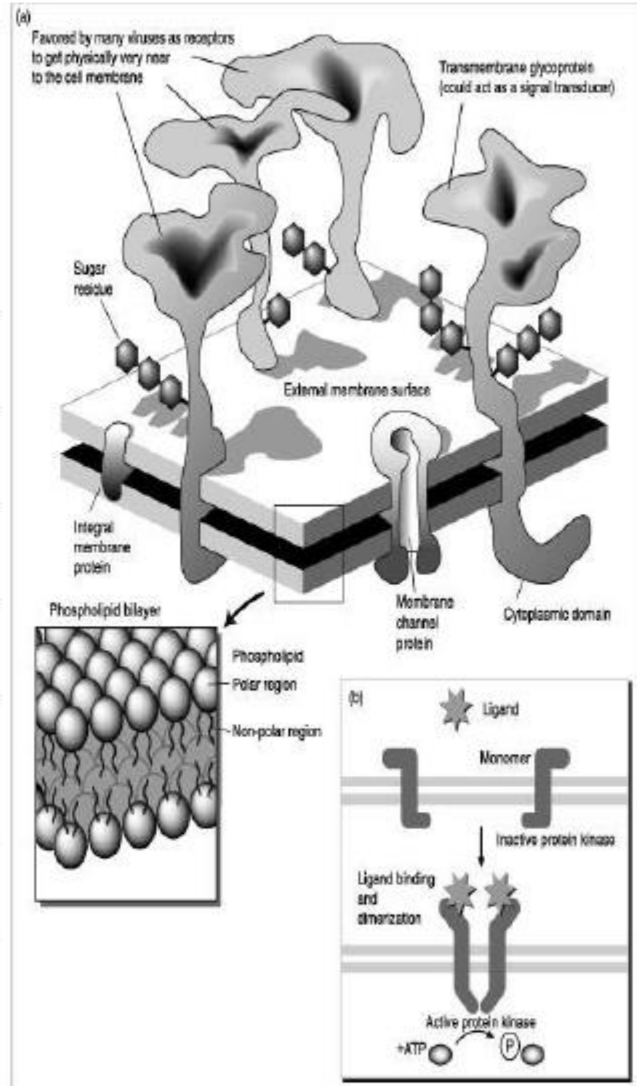
BASIC STEPS IN VIRAL LIFE CYCLE

- ADSORPTION
- PENETRATION
- UNCOATING AND ECLIPSE
- SYNTHESIS OF VIRAL NUCLEIC ACID AND PROTEIN
- ASSEMBLY (maturation)
- RELEASE

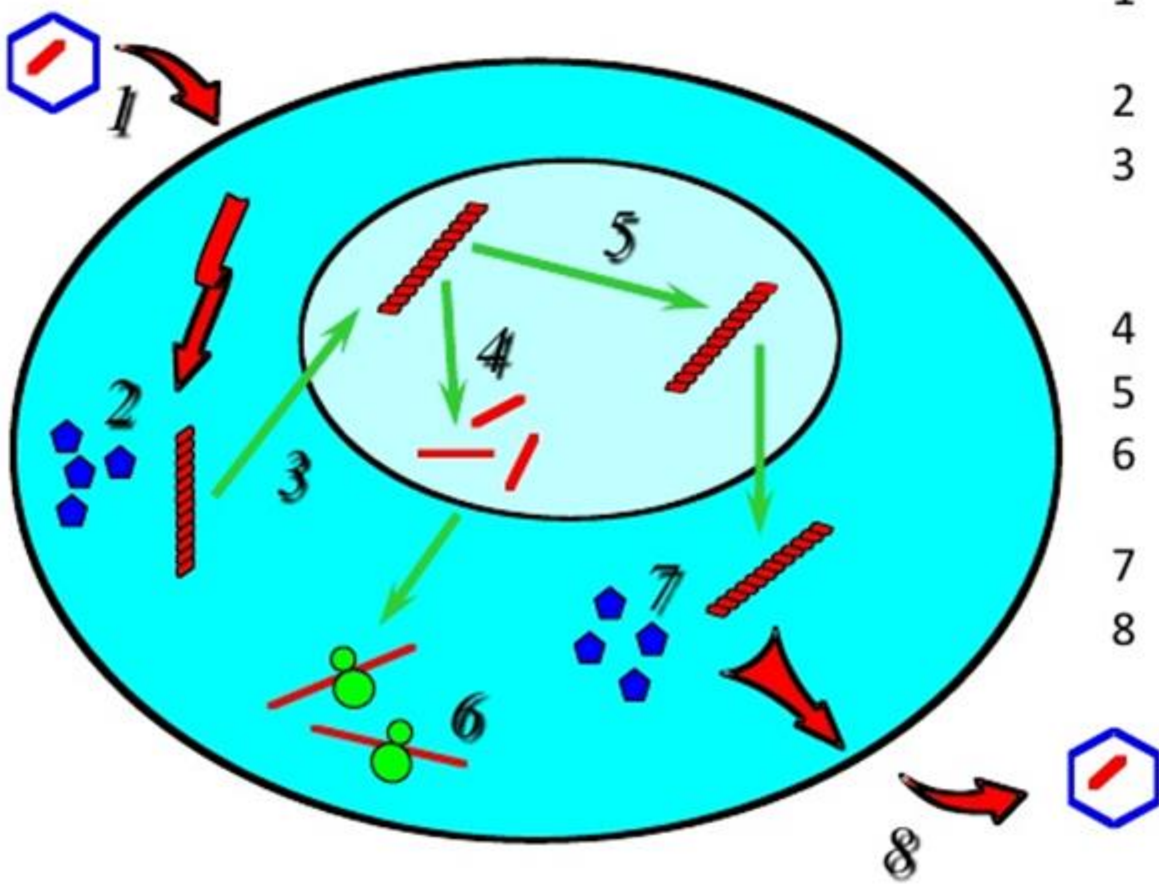
Viral replication: Viruses are the ultimate parasite. They are totally dependent on a host cell to replicate (make more copies of itself).

- **Adsorption**: The surface of the virion contains structures that interact with molecules (receptors) on the surface of the host cell. This is usually a passive reaction (not requiring energy), but **highly specific**. It is the specificity of the reaction between viral protein and host receptor that defines and limits the host species and type of cell that can be infected by a particular virus. Damage to the binding sites on the virion or blocking by specific antibodies (neutralization) can render virions non-infectious.
- **Uptake**: The process whereby the virion enters the cell. It occurs either as a result of **fusion** of the viral envelope **with the plasma membrane** of the cell or else by means of **endocytosis**.
- **Uncoating**: Once inside the cell, the **protein coat of the virion dissociates** and the viral genome is released into the cytoplasm.
- **Early phase**
  Once the genome is exposed, **transcription of viral mRNA** and translation of a number of **non-structural** ("early") **proteins** takes place. The function of these is to replicate the viral genome.
- **Genome replication**
  Multiple copies of the viral genome are synthesized by a viral polymerase (one of the "early" proteins).
- **Late phase**
  Transcription and translation of viral mRNA and **synthesis of the structural** ("late") **proteins** which are needed to make new virions.
- **Assembly of new virions**
  Assembly of new viral capsids takes place either in the nucleus (e.g. herpesviruses) or in the cytoplasm (e.g. poliovirus) of the cell, or sometimes, just beneath the cell surface (e.g. budding viruses such as influenza). The proteins self assemble and a genome enters each new capsid.
- **Release of progeny virions**
  Release of new infectious virions is the final stage of replication. This may occur either by budding from plasma membrane or else by disintegration (lysis) of the infected cell. Some viruses use the secretory pathway to exit the cell: virus particles enclosed in *golgi*-derived vesicles are released to the outside of the cell when a transport vesicle fuses with the cell membrane.

RECEPTOR	VIRUS
ICAM-1	polio
CD4	HIV
acetylcholine	rabies
EGF	vaccinia
CR2/CD21	Epstein-Barr
HVEM	herpes
Sialic acid	Influenza, reo, corona

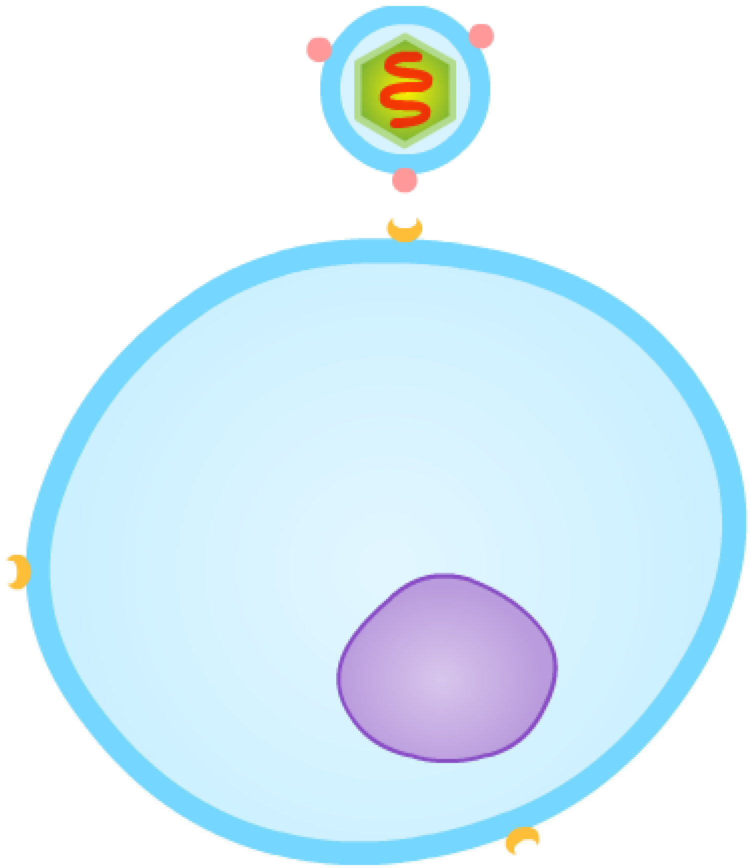


Virus Replication

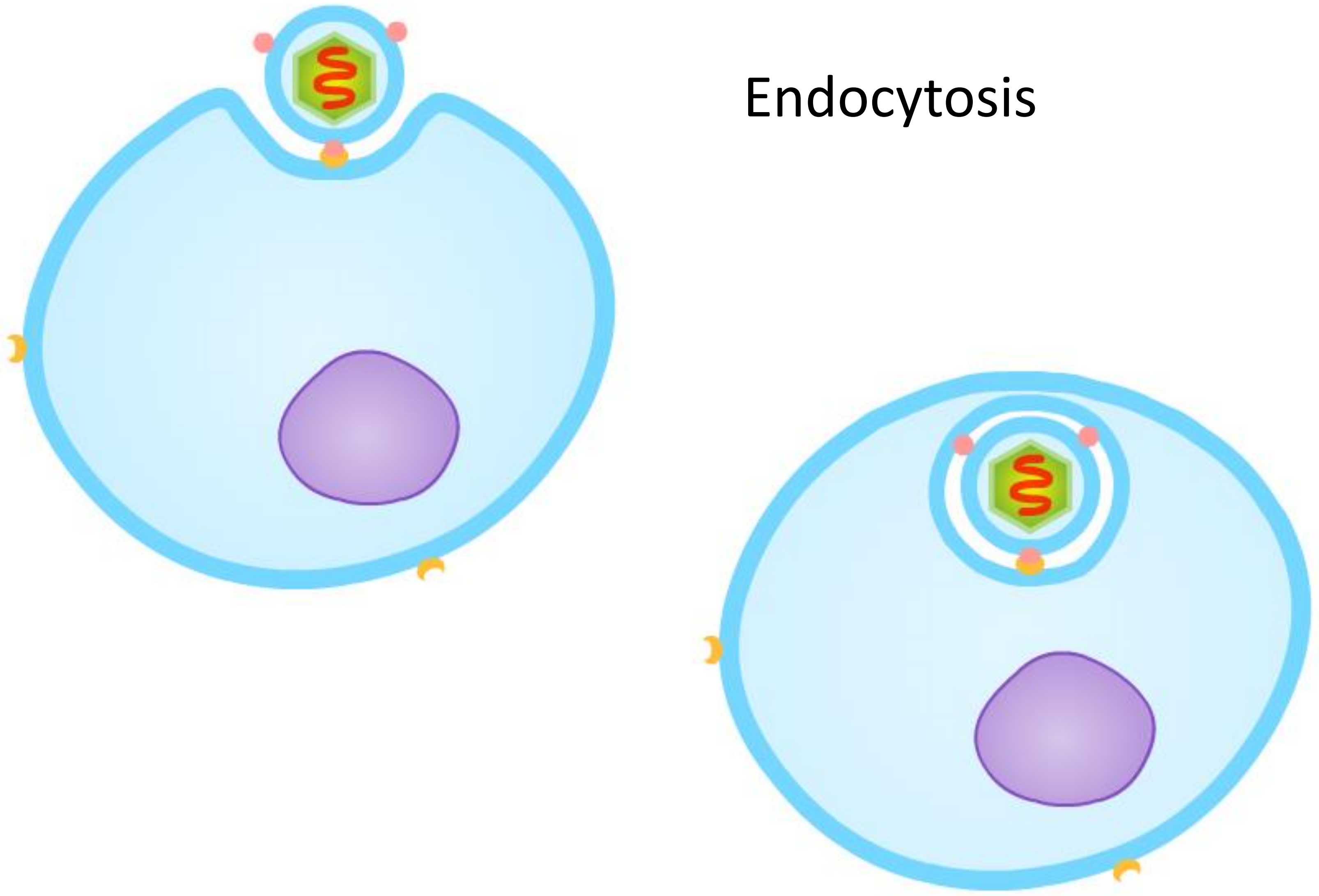


1 Virus attachment and entry
2 Uncoating of virion
3 Migration of genome nucleic acid to nucleus
4 Transcription
5 Genome replication
6 Translation of virus mRNAs
7 Virion assembly
8 Release of new virus particles

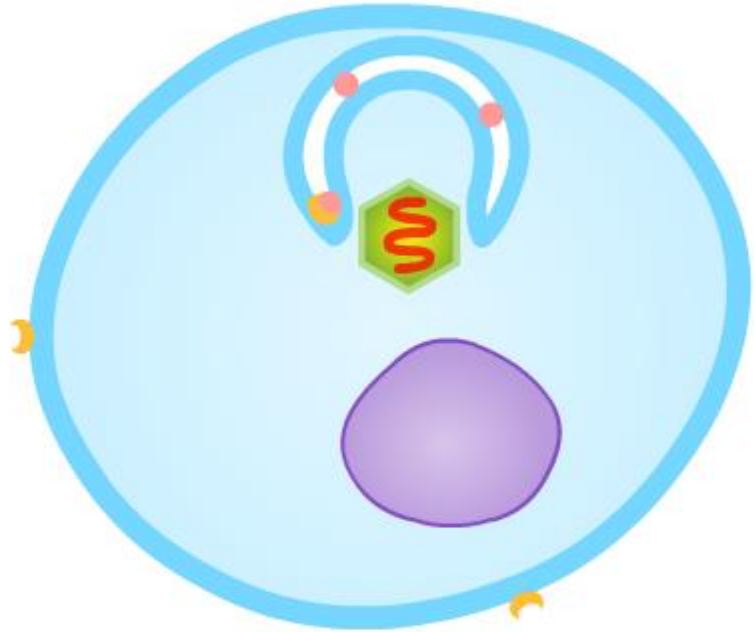
Attachment

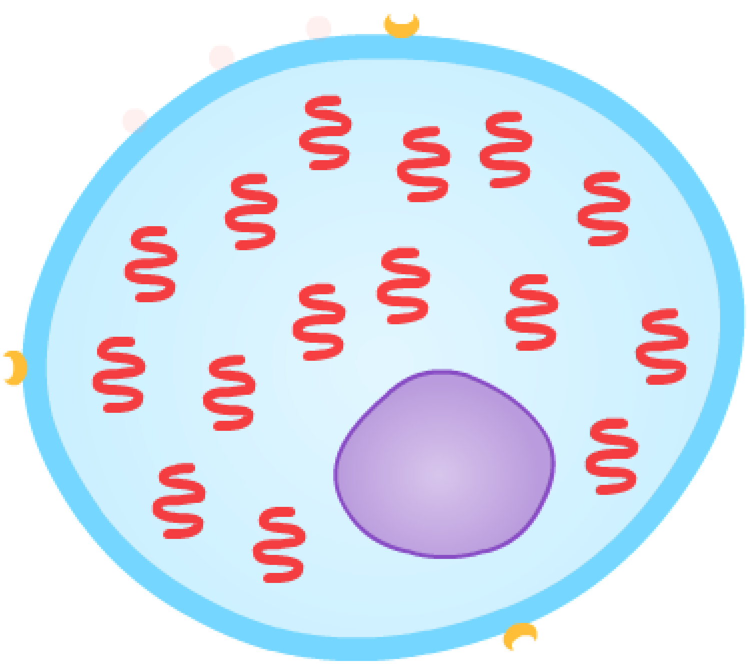


Endocytosis



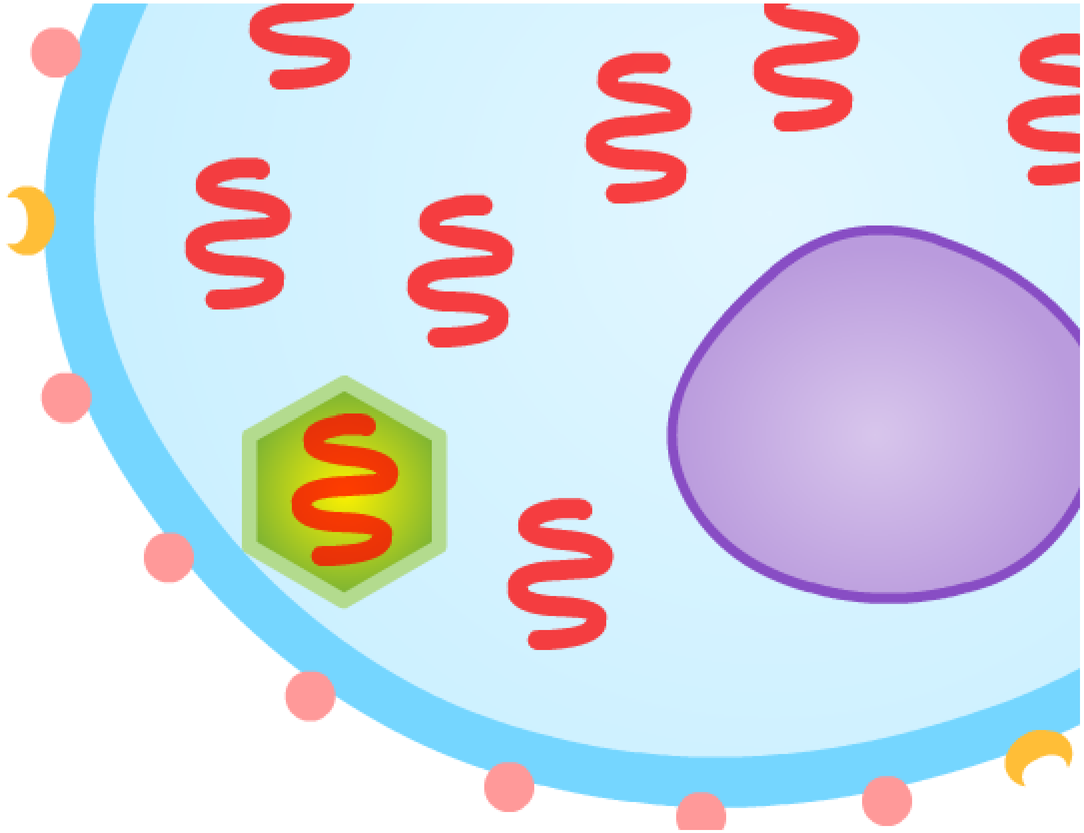
Uncoating



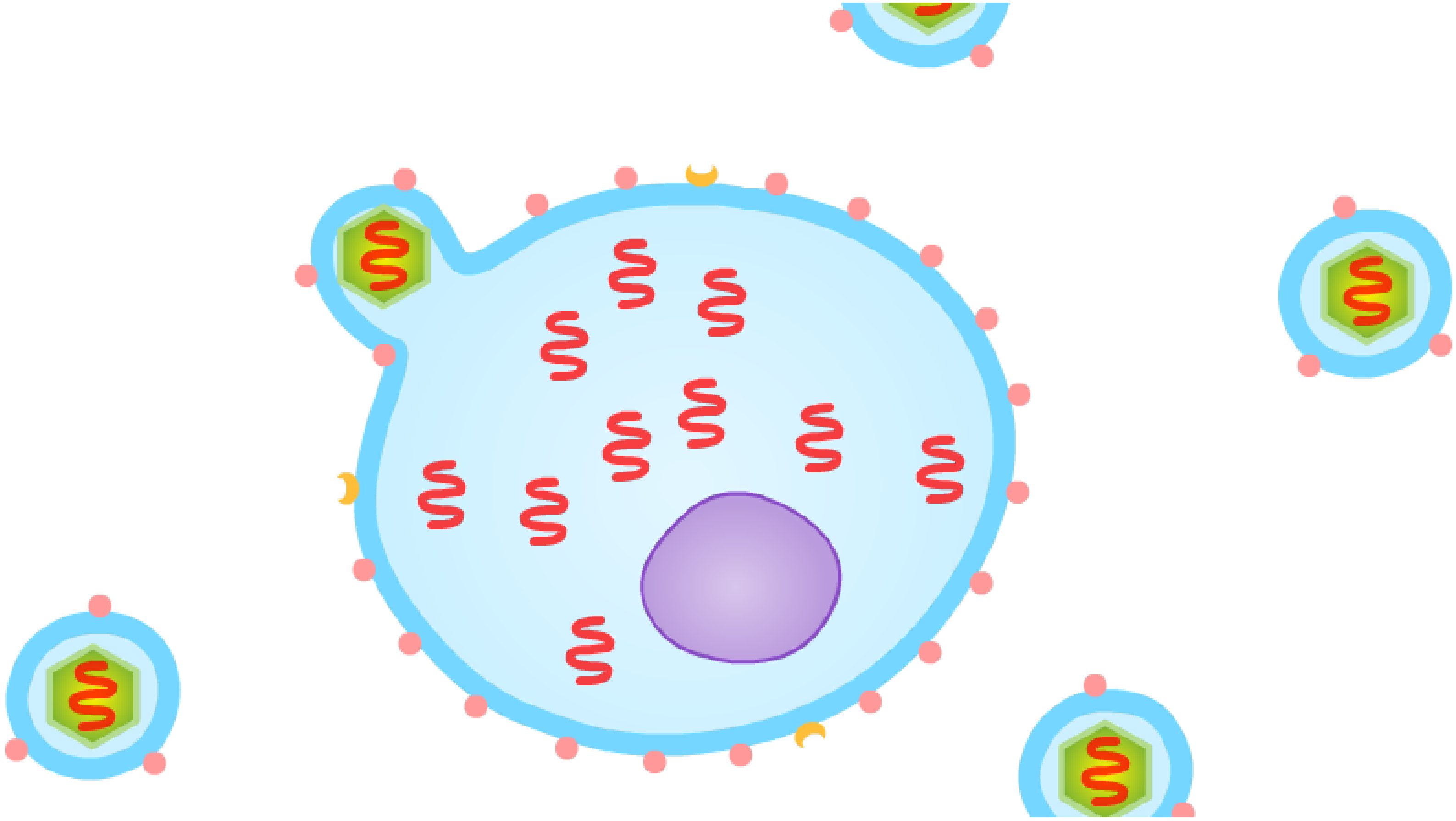


Replication

Assembly and maturation



Release of new viruses



Transmission of Viruses

- Respiratory transmission
  - Influenza A virus
- Faecal-oral transmission
  - Enterovirus
- Blood-borne transmission
  - Hepatitis B virus
- Sexual Transmission
  - HIV
- Animal or insect vectors
  - Rabies virus

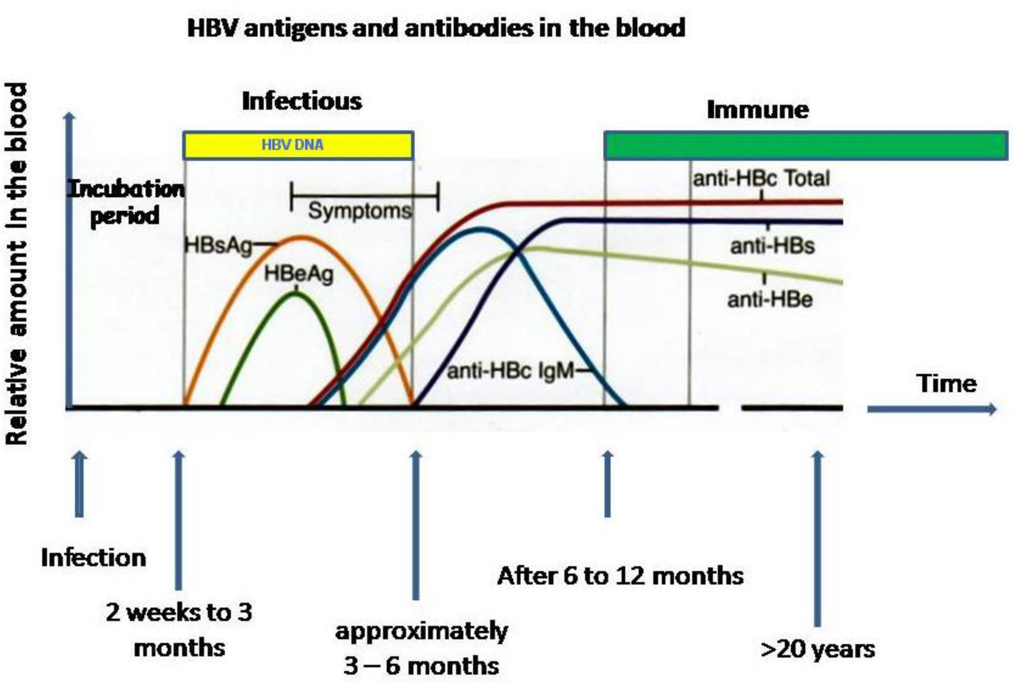
How do viruses cause disease?

- Viruses are capable of infecting **all types of living organism** from bacteria to humans, (including plants and insects!). A major factor that controls which cell type a virus can infect (cell tropism) is the presence (on the cell surface) of the appropriate receptor, to which the virus must attach in order to gain entry into the cell.

- Viruses enter the body by **inhalation, ingestion, sexual intercourse** or **inoculation** through the skin or mucous membranes. Infection may also sometimes be passed from a mother to her foetus t**ransplacentally** (vertical transmission**)**. Once a virus has gained entry into the body, infection may either remain **localised** to the site of entry (an example of this is influenza where the virus remains confined to the respiratory tract), or it may cause a **disseminate**d infection. Here, the virus replicates initially at the site of entry, but then enters the blood (**viraemia**) or lymphatics and spreads throughout the body (e.g. Measles). Other viruses such as Rabies and Herpes Simplex may replicate locally initially, then enter **nerve** endings and travel up the axon to infect the **central nervous system**.

How do viruses cause disease?

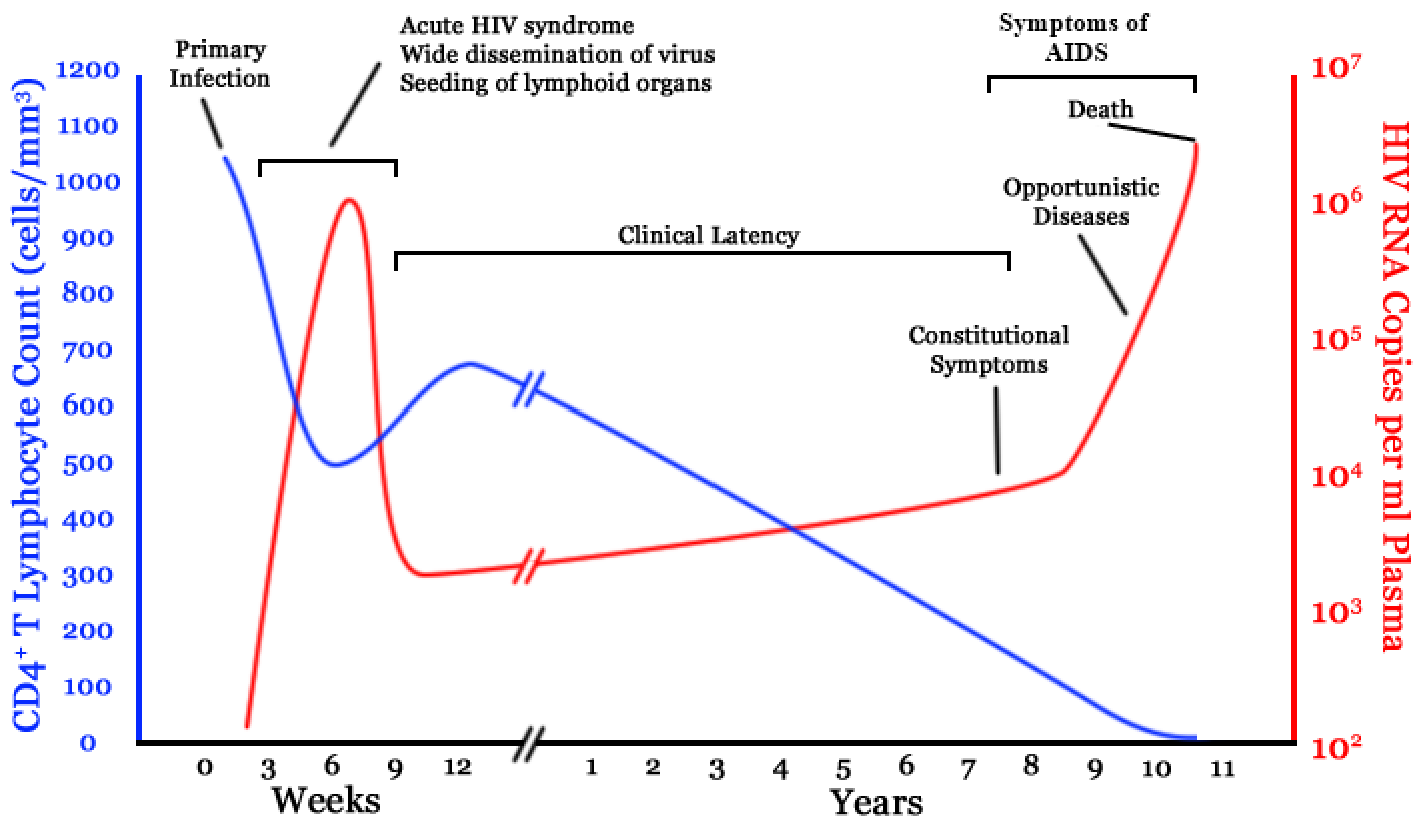
- The term **incubation period** defines the time from exposure to an organism to the onset of clinical disease. In general, viruses that cause **localized** infections have **short** incubation periods (<7 days), while in **disseminated** infections, the incubation period tends to be **longe**r.



- **Both viral and host factors** contribute to clinical disease during the course of a viral infection. Host immune cells release interferons and other cytokines which induce the symptoms of fever and malaise. Tissue specific damage may be due to **virus-induced lysis** of infected cells or due to inflammation and destruction of infected cells by the host's **immune response**. Because viruses replicate **intra-cellularly**, recovery from a viral infection requires the action of **specific cyto-toxic T lymphocytes** which recognise and eliminate virus-infected cells. Virus-specific antibody levels rise during the course of the infection, but antibody plays only a limited role in recovery from an established infection for most viruses. Nonetheless specific **antibody** plays a very important role in **preventing re-infection** of the host with the same virus.

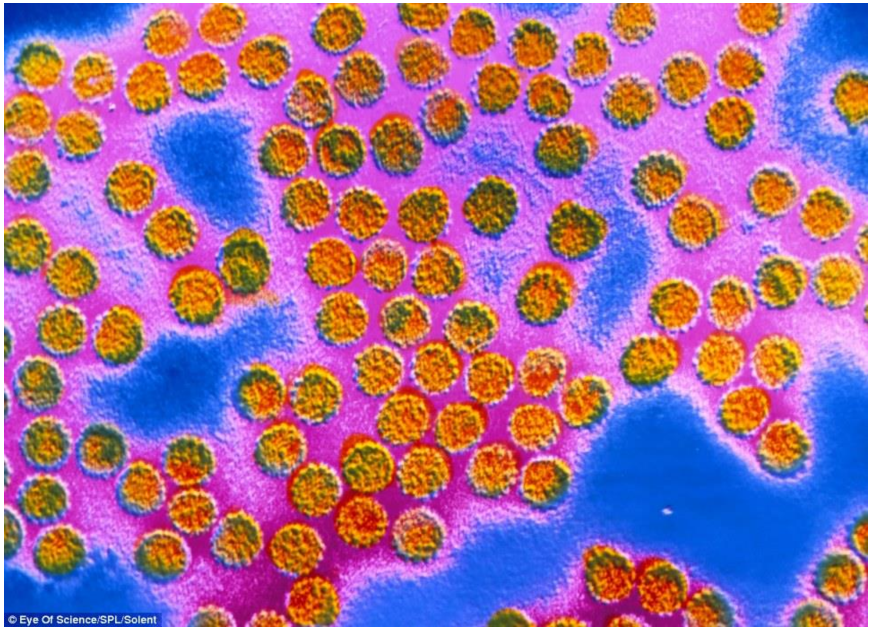
How do viruses cause disease?

- An effective immune response can eliminate most viruses from the body and thus most viral infections are short lived. However, there are certain viruses that are able to evade the immune response and establish **persistent infections** in their host.
- The most famous example of such a virus is HIV, but there are many others. Viruses use a variety of strategies to evade the immune system. On the whole, these persistent infections are asymptomatic and only manifest clinically if the patient becomes immuno-compromised.



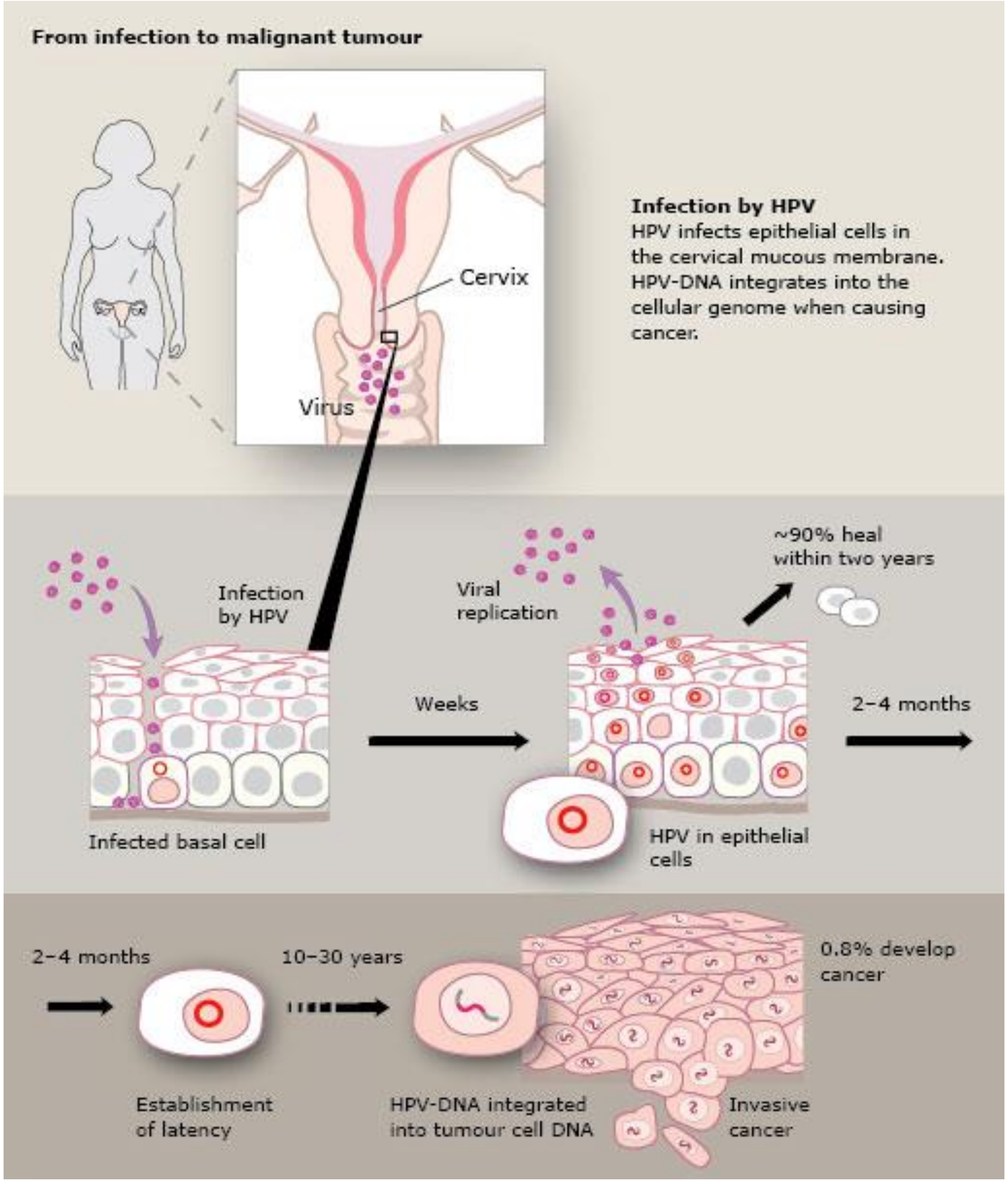
Viruses and cancer:

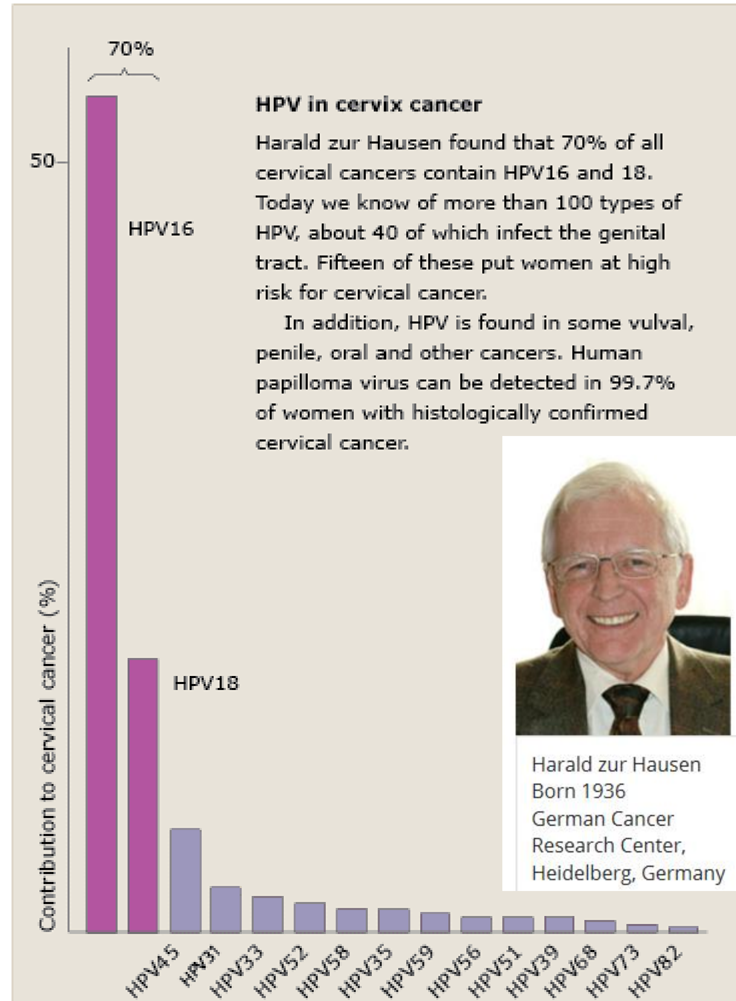
- About 15% of human cancers are caused by viruses. Certain persistent viruses survive in the host by transforming the cells they infect (inducing infected cells to proliferate). However, the virus infection is only the first step in the pathway to malignancy and only a small percentage of infected people actually get cancer.
- Common virus-induced cancers include: carcinoma of the **cervix (Human papillomavirus)**, liver cancer (hepatitis B and C), Kaposi sarcoma (human herpesvirus 8) and Burkitts lymphoma (Epstein Bar virus).



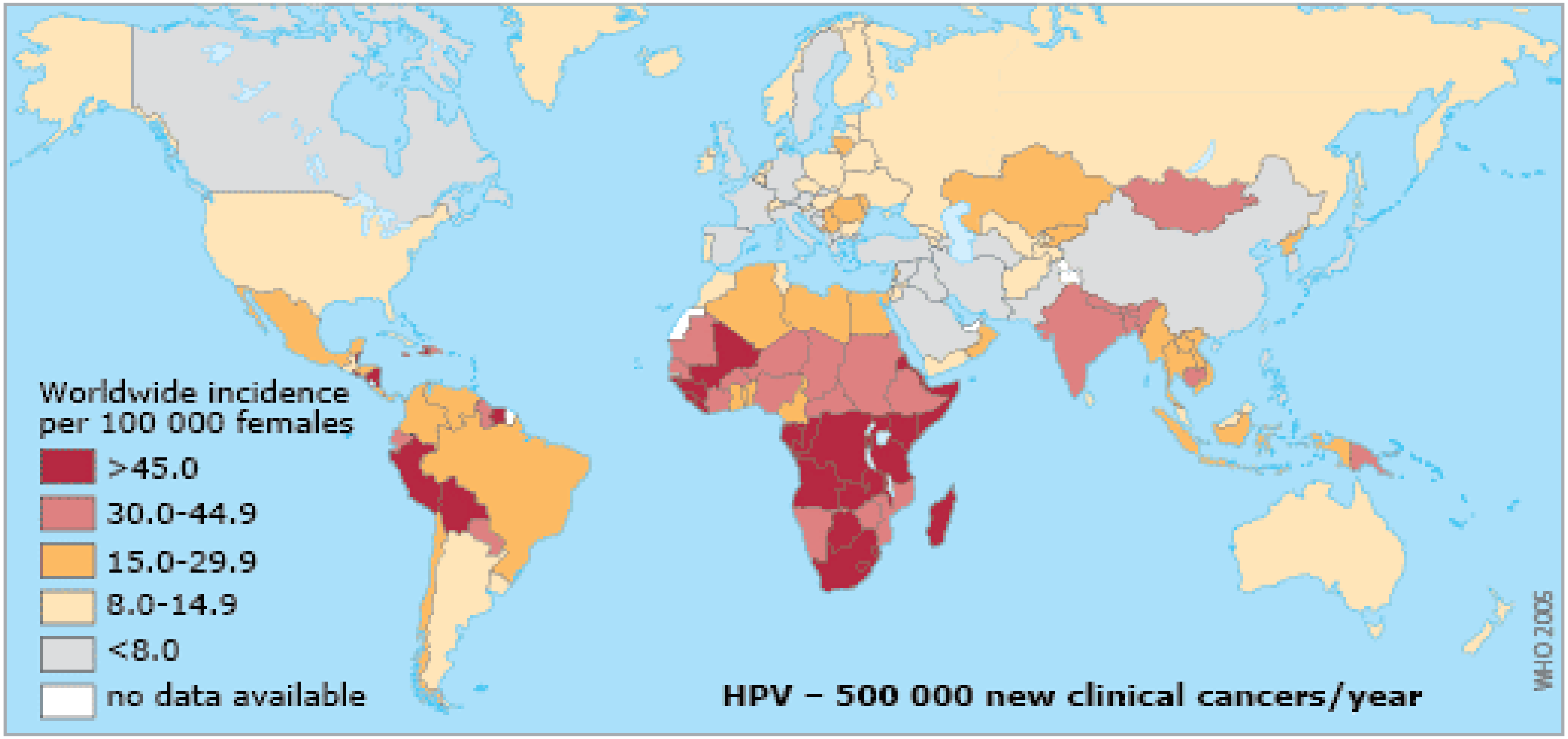
Human papillomavirus (HPV)

Nobel Prize in Physiology or Medicine 2008





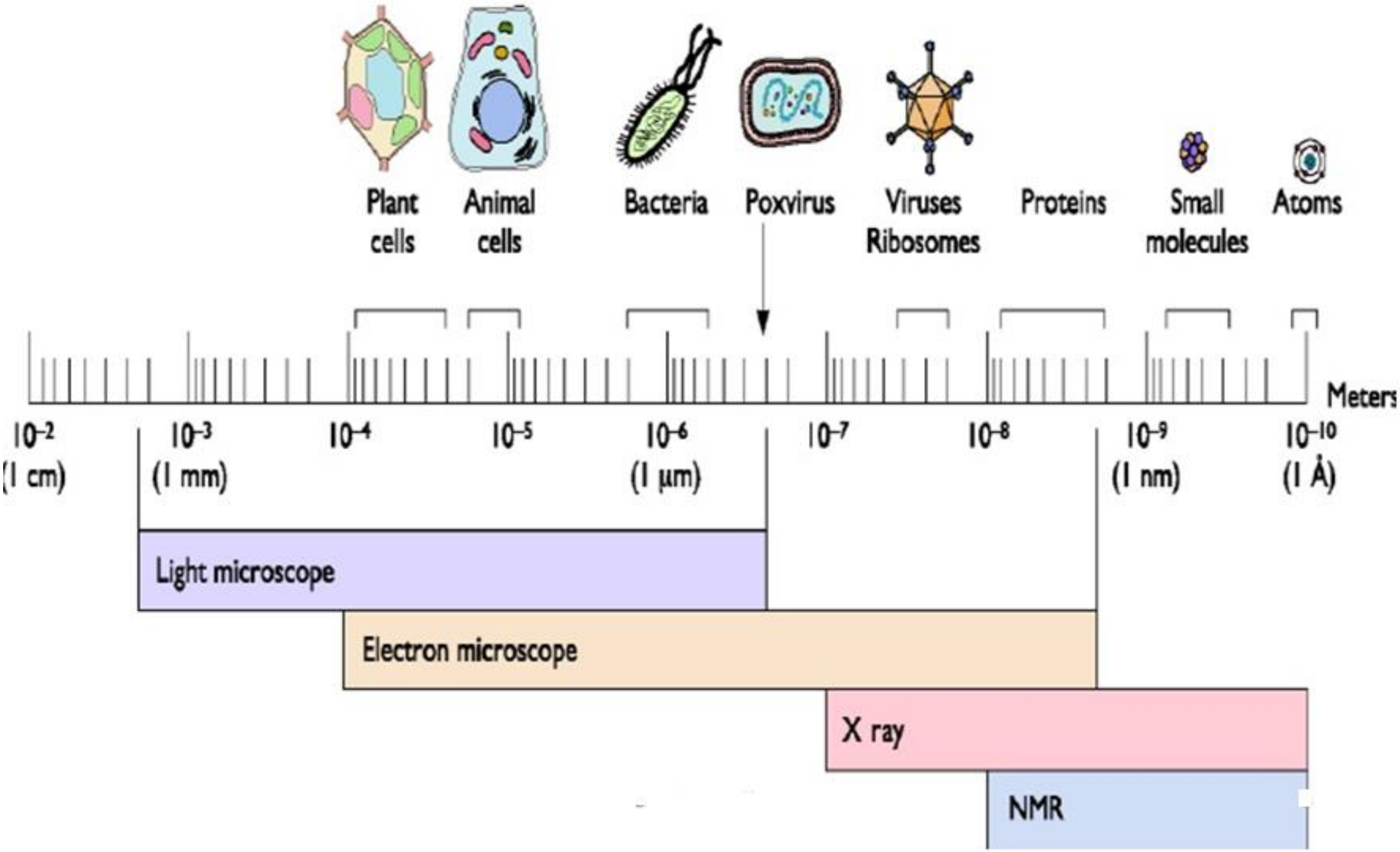
Distribution of cervical cancer due to HPV



What is a virus?

- They have **no organelles**.
- They are very **small**, sizes range from 20 to 200 nm. This is beyond the resolving power of the light microscope.

The size of viruses



Disinfection and inactivation of viruses:

Heat; Most are inactivated at 56 °C for 30 minutes or at 100 °C for a few seconds
Drying Variable; enveloped viruses are rapidly inactivated.
Ultra-violet irradiation; Inactivates viruses
Organic solvents (Chloroform, Ether, Alcohol); Enveloped viruses are inactivated; those without are resistant.
Oxidizing and reducing agents; Viruses are inactivated by formaldehyde, chlorine, iodine and hydrogen peroxide
Phenols; Most viruses are resistant

Sub-viral agents

- **Satellites**
  - Contain nucleic acid
  - Depend on co-infection with a helper virus
  - May be encapsidated (satellite virus)
  - Mostly in plants, can be human e.g. hepatitis delta virus
  - If nucleic acid only = virusoid
- **Viroids**
  - Unencapsidated, small circular ssRNA molecules that replicate autonomously
  - Only in plants, e.g. potato spindle tuber viroid
  - Depend on host cell polII for replication, no protein or mRNA
- **Prions**
  - No nucleic acid
  - Infectious protein e.g. BSE