The viral cycle overview

1. **Attachment**
2. **Entry (uncoating)**
3. **Transcription**
4. **Translation**
5. **Genoma Replication**
6. **Assembly (and Maturation)**
7. **Exit (Egress)**

Viral (life?) cycle entails all steps beggining from an entry of a viral particle (virion) into a host cell until the exit of new virions from that cell.

What is the difference between a viral particle and a virion?

1. The entry (and attachment) of the virus into the cell is an active process!

Reaching the genome replication site (entry) includes:

endocytosis,

membrane fusion,

movement of vesicles within the cell,

entry into the nucleus for some viruses.

1. **Attachment** (of a virus to the surface of target cells):

On the surface of the virus are attachment structures -virus (glyco) proteins, “antireceptors”, and on the cell surface are receptors that correspond to them in structure and charge.

Capsid or envelope (glyco)proteins (peplomeres, spikes, projections) are important for the attachment.

• Phages – host range/specificity of a virus is determined on the level of attachment.

• Phyto- and Mycoviruses regulate host range differently.

• Animal viruses – attachment mostly determines host specificity, but virus tropism too (tissue and cell types where a virus can invide and replicate therein).

Do all viruses attach to the cell surface prior to entry?

• Plant virus specificity is determined at the genome transcription (replication) level.

TMV-A replicates in tomato  RNA TMV-A + capsid TMV-B

TMV-B no replication  RNA TMV-B + capsid TMV-A

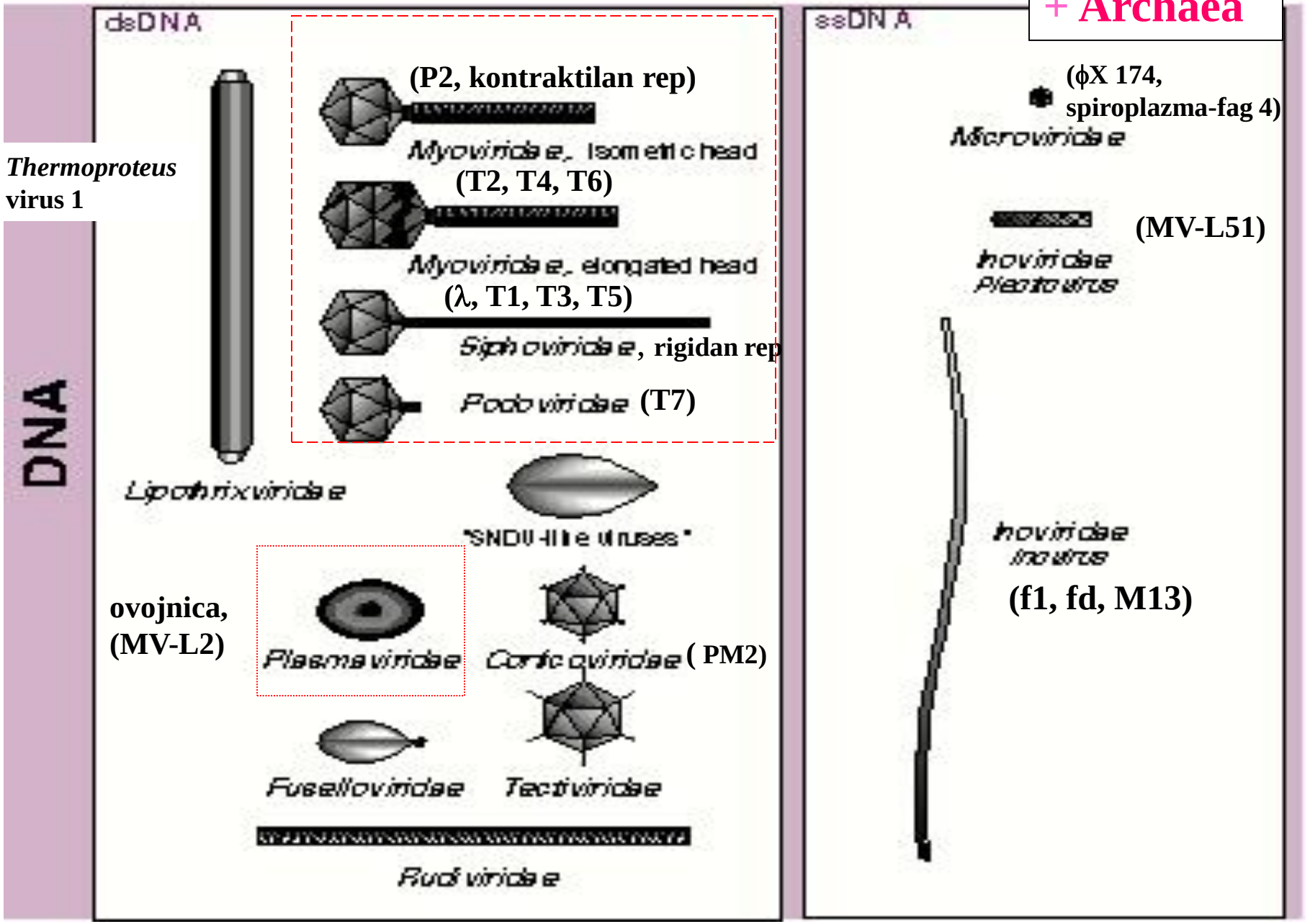
- Phytoviruses have a specific problem to solve – virrion passage to new host cells inside a plant host. Why?
- Solutions:

a) Only a genome is transported (+RNA) aided by a movement protein (MP) through plasmodesmata,

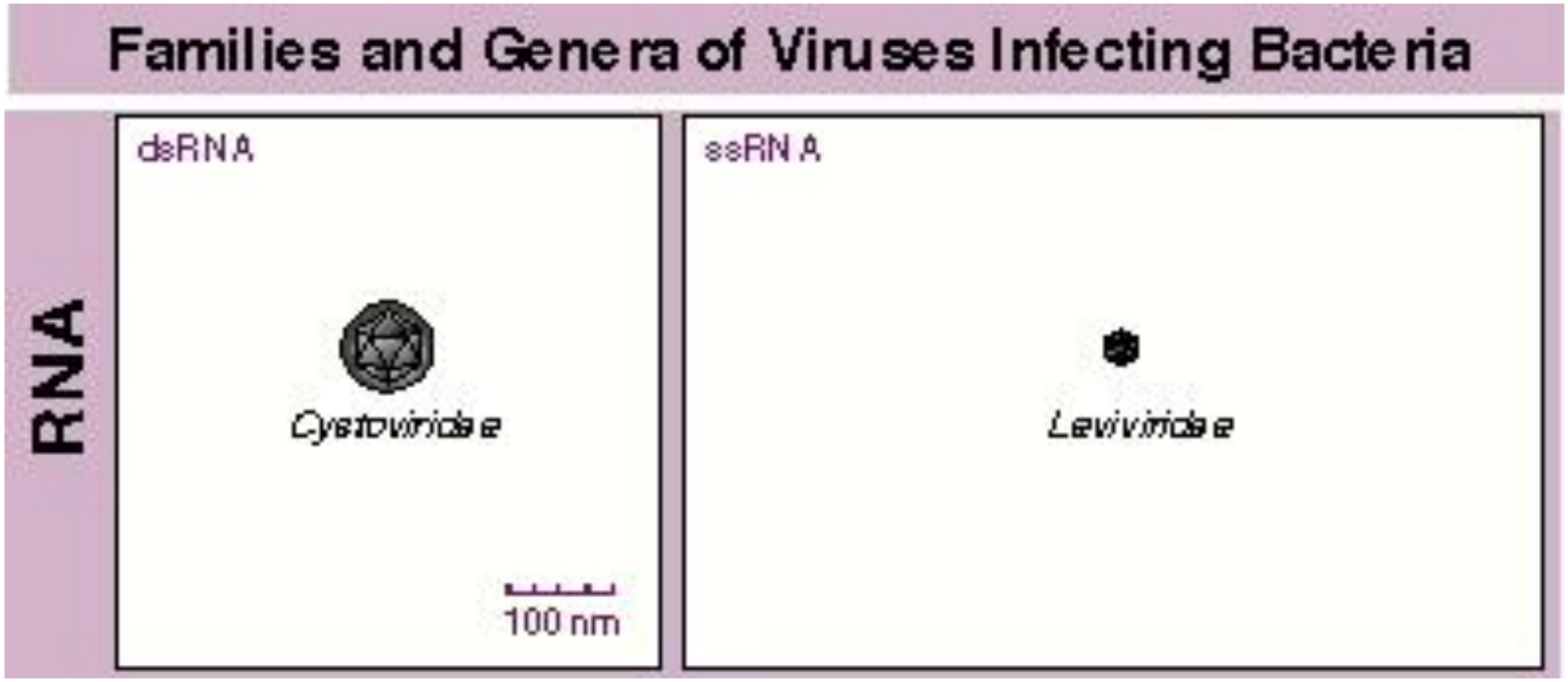
b) or a whole virion is trafficked through tubules inserted into plasmodesmata to enlarge them (enlarging *size exclusion limit*).

Families and Genera of Viruses Infecting Bacteria

+ Archaea



Thermoproteus virus 1



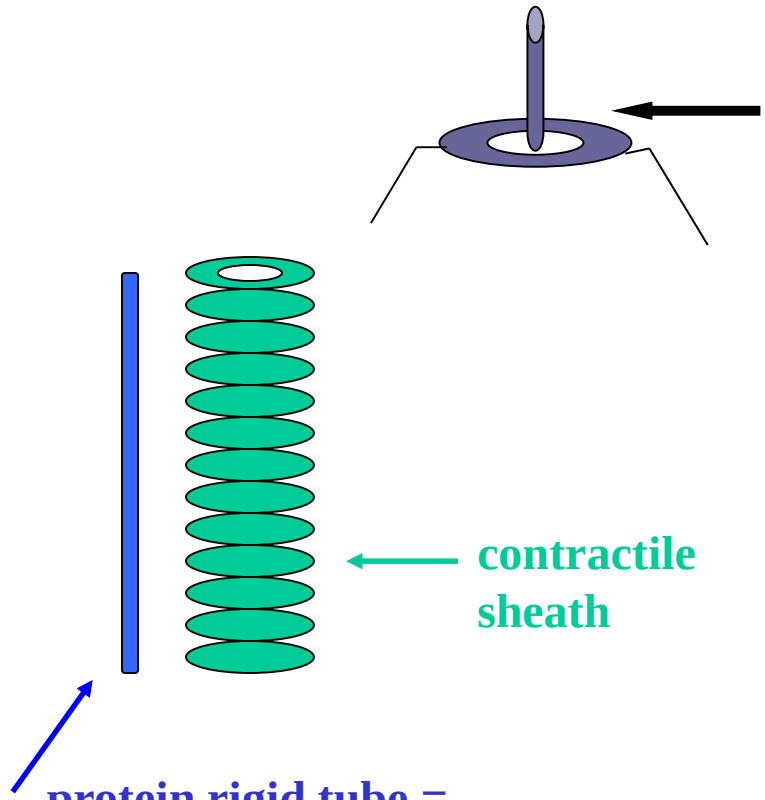
capsid+envelope, ϕ6

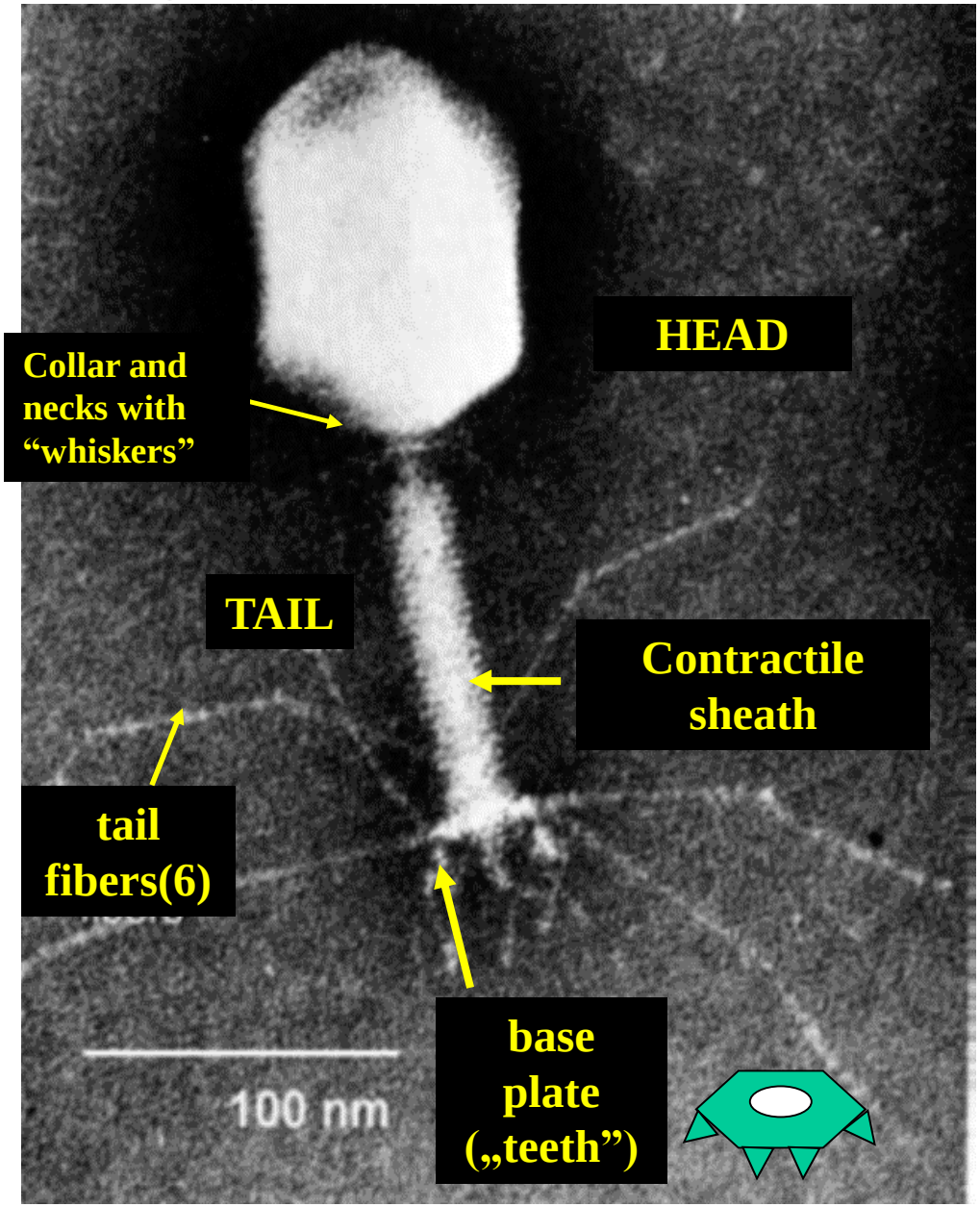
unenveloped, MS2, Qß, f2

- Phage attachment depends on the phage type

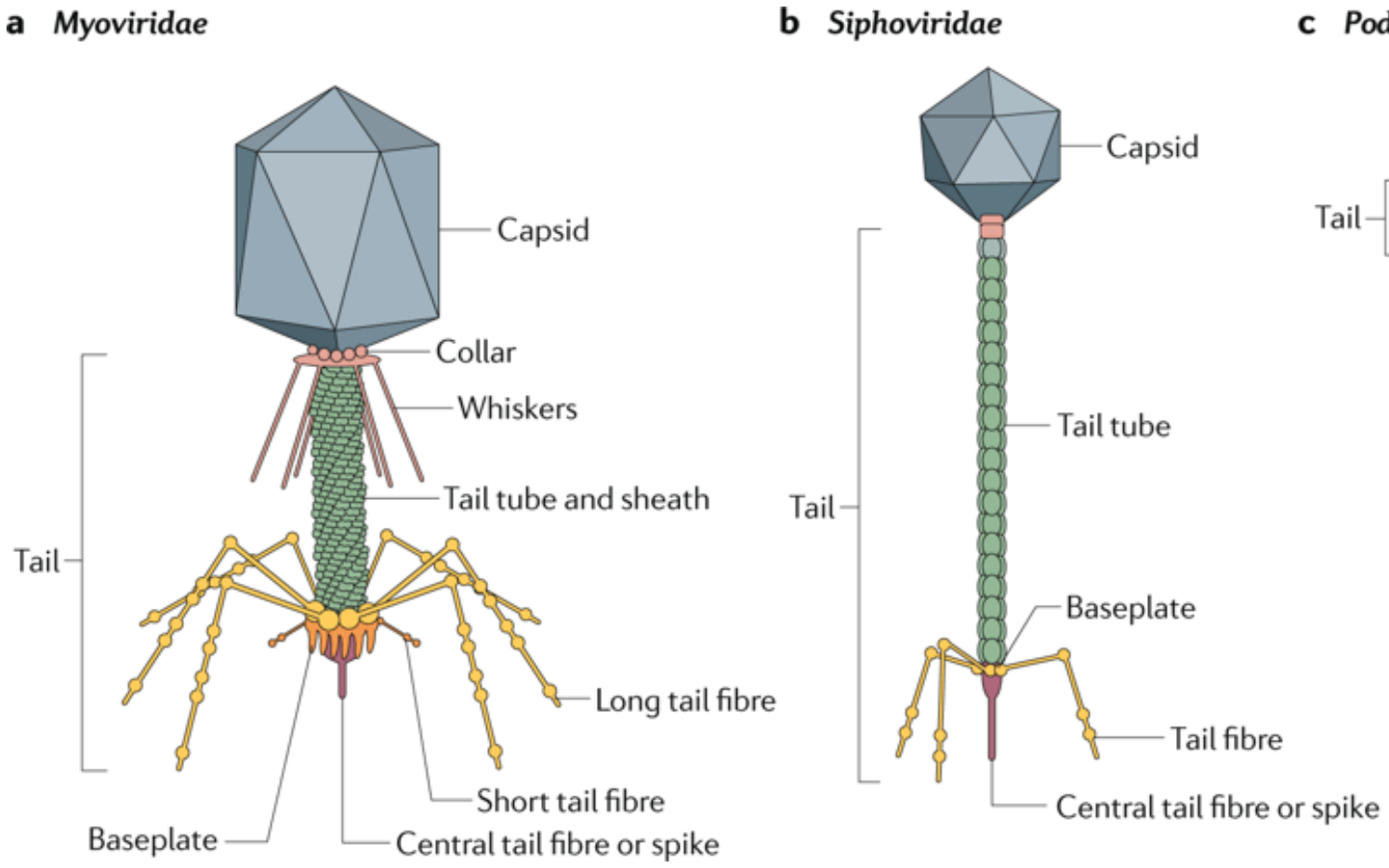
T4 coliphage – d = 80 nm, l = 200 nm

Escherichia coli strain B

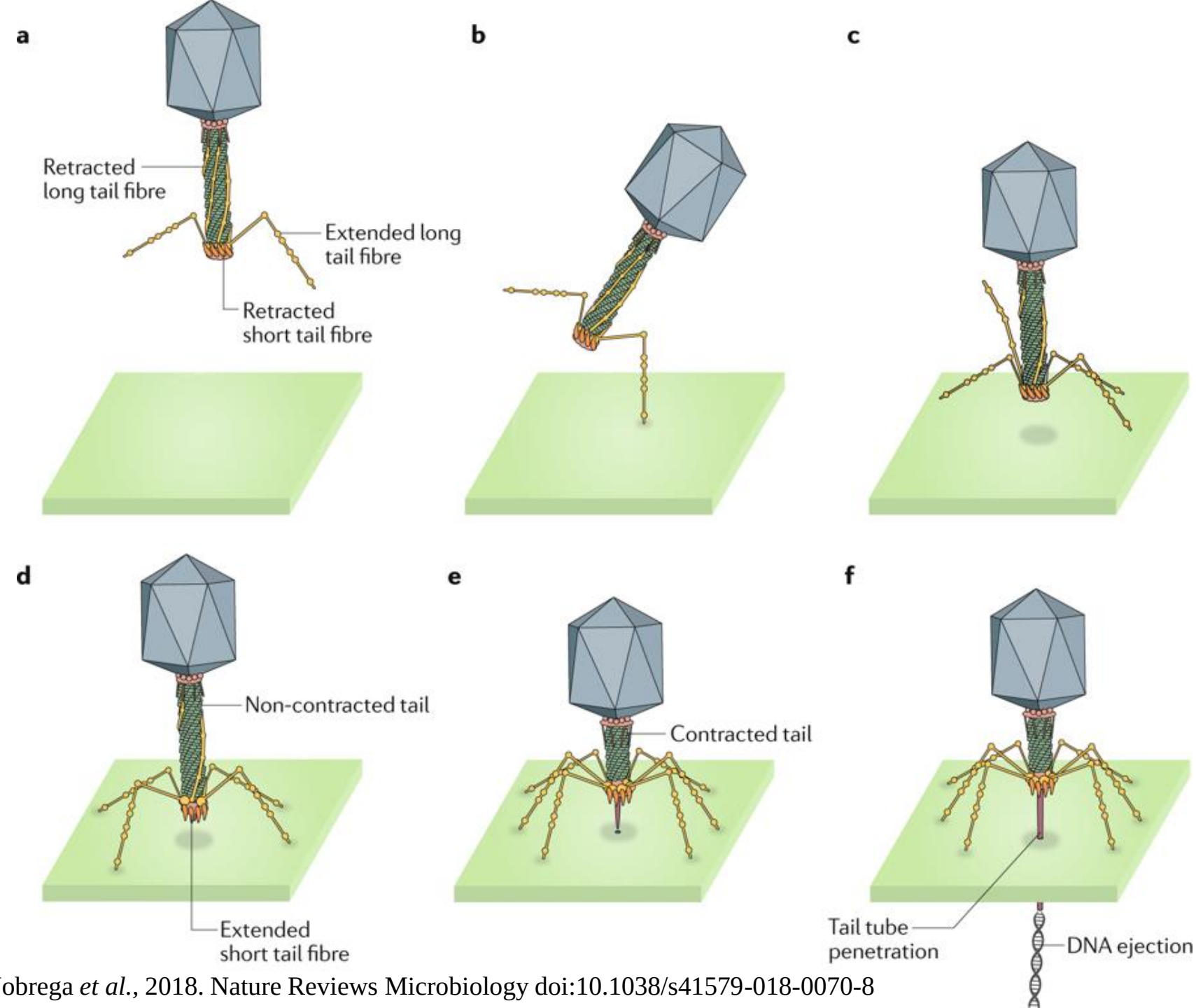




Attachement in phages is irreversible after docking firmly (enhanced by cathions Mg^{2+}, Ca^{2+}), in T4, Trp helps extending tail fibers.



Nobrega *et al.*, 2018. Nature Reviews Microbiology doi:10.1038/s41579-018-0070-8

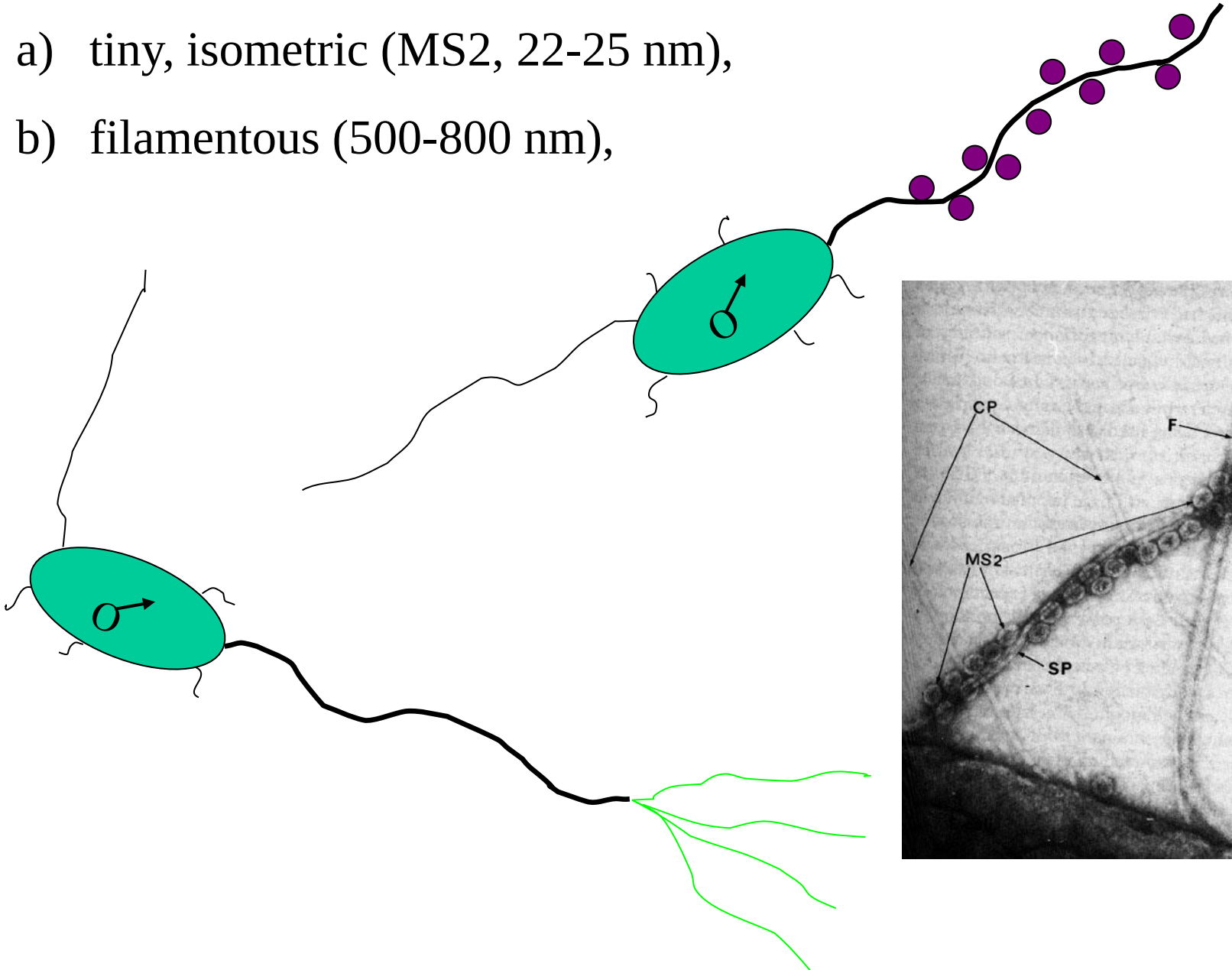


Nobrega *et al.*, 2018. Nature Reviews Microbiology doi:10.1038/s41579-018-0070-8

Androphage attachment:

a) tiny, isometric (MS2, 22-25 nm),

b) filamentous (500-800 nm),



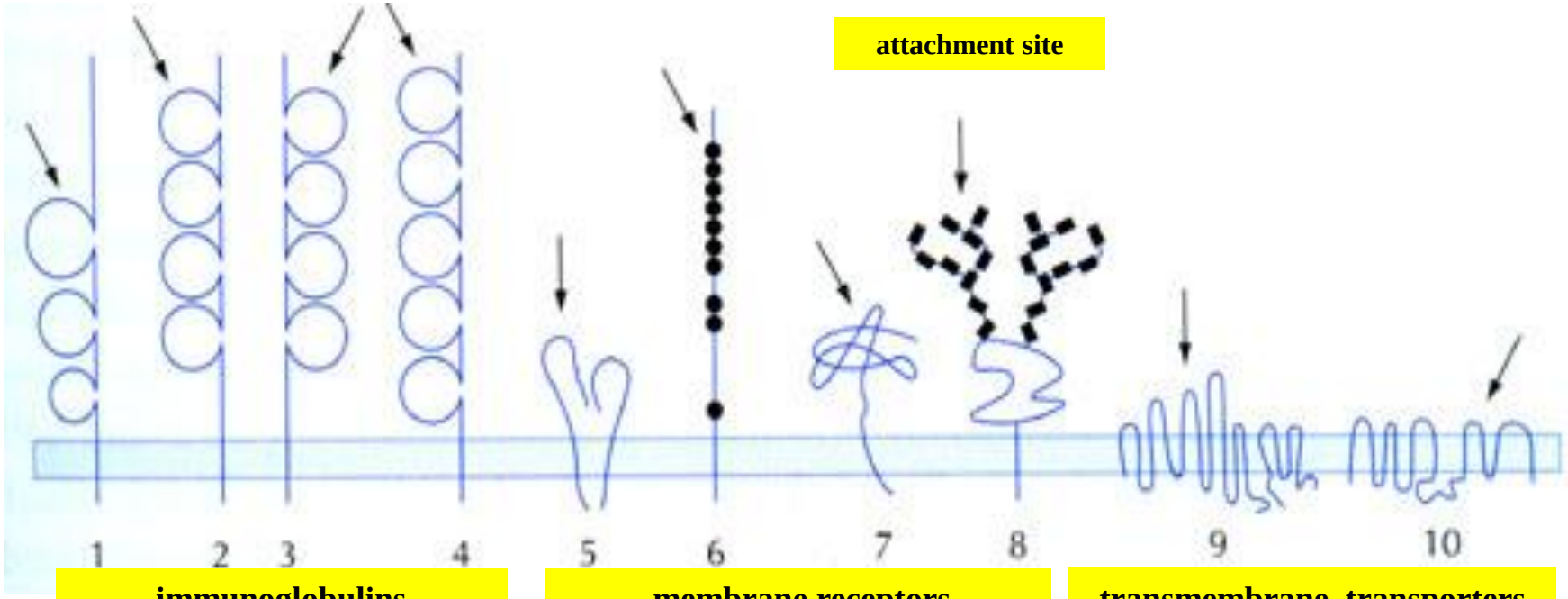
What type of molecules are cell receptors?

Proteins (usually glycoproteins - specific receptors) or carbohydrate components of them or glycolipids (less specific).

One virus species can use more than one receptor (herpes virus).

Different viruses can use the same receptor.

Some viruses need a receptor and a coreceptor (HIV-1).



1- PVR (=CD155), poliovirus

2- CD4, HIV

3- carcinoembriogenic antigens , coronaviruses

4- ICAM-1, rhinoviruses

5- VLA-2 integrin, echoviruses

6- LDL-receptor, rhinoviruses

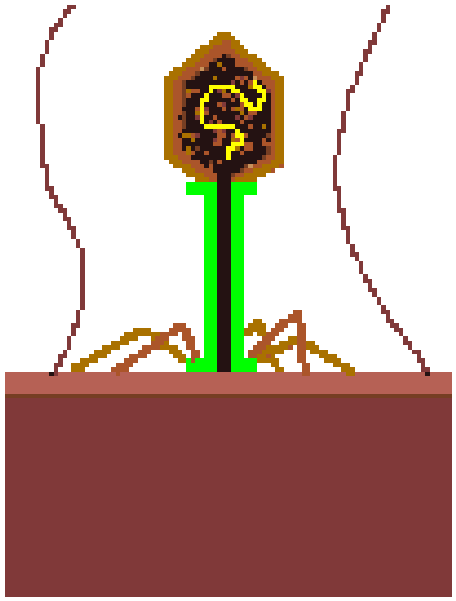
7- aminopeptidase N, coronaviruses

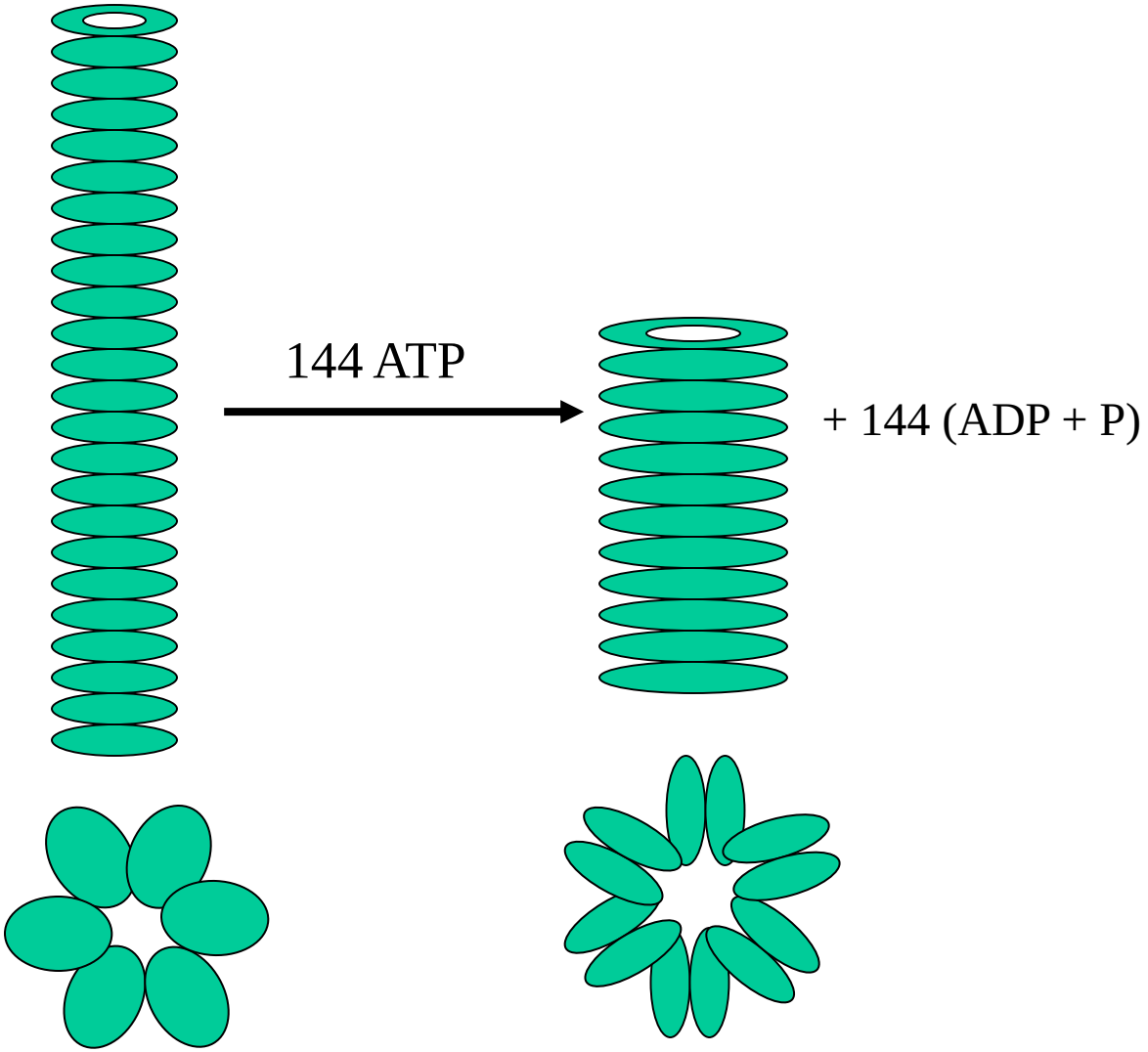
8- sialic acid - influenza, reoviruses, rotaviruses

9- cation transporter of amino acid, murine leukemia virus

10- Na- dependent phosphate receptor, gibbon leukemia virus

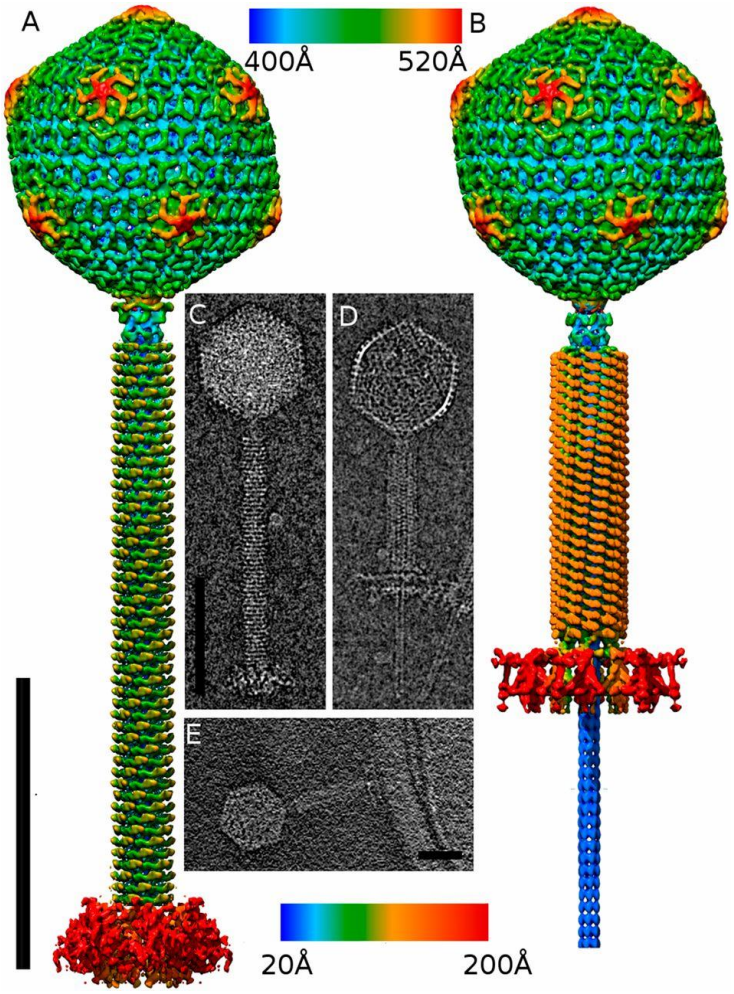
2. Entry (penetration) – a genome enters the cell, immediately after attachment, only in live cells (energy!). Mostly in cytoplasm,but some travel to nucleus or to other places?





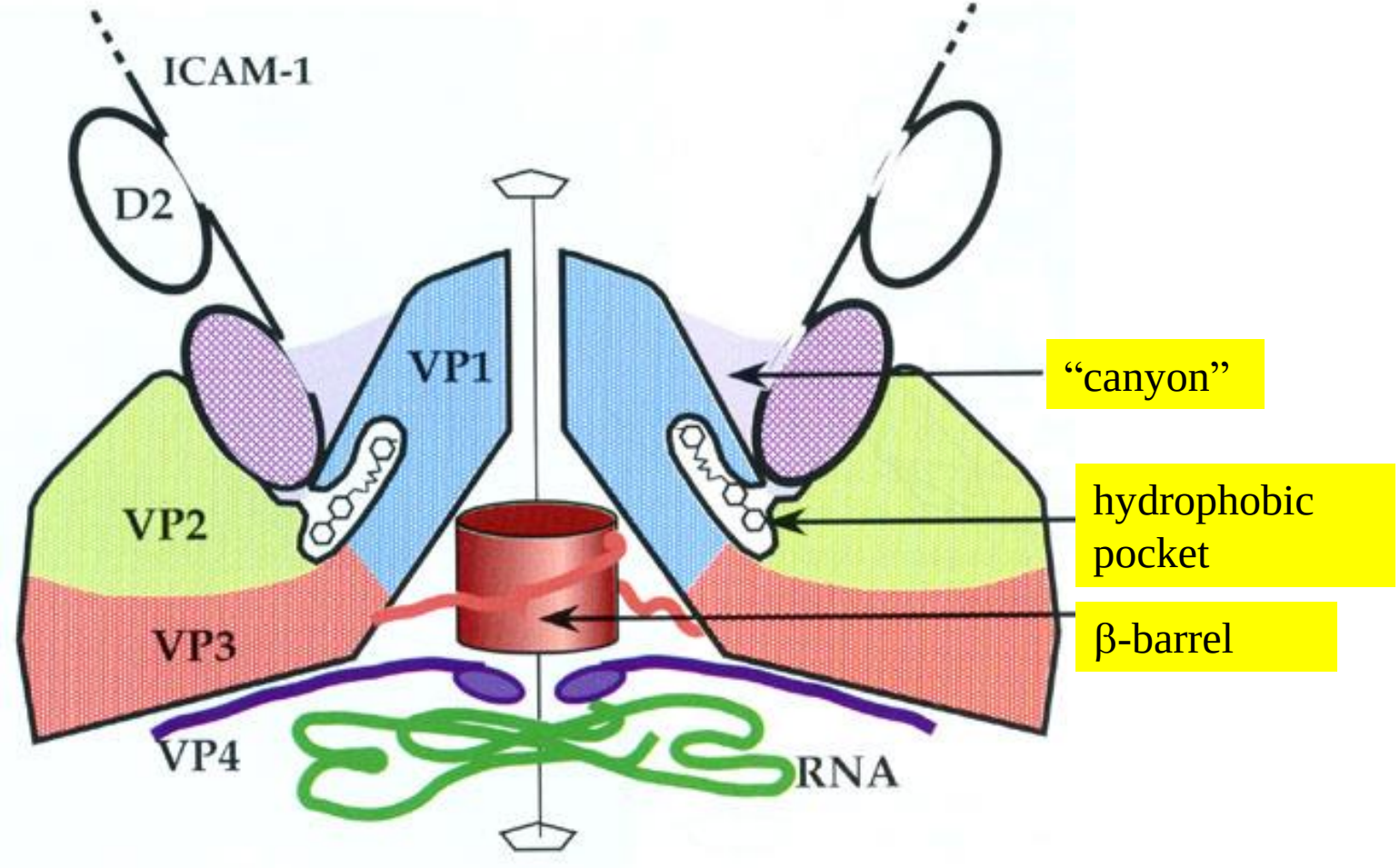
Phage chemically and physically disrupts bacterial cell wall (on glycoside bond between N-acetyl muraminic acid and N-acetyl glucosamine).

Virions of bacteriophage phi812 in native conformation (A) and after tail contraction (B).

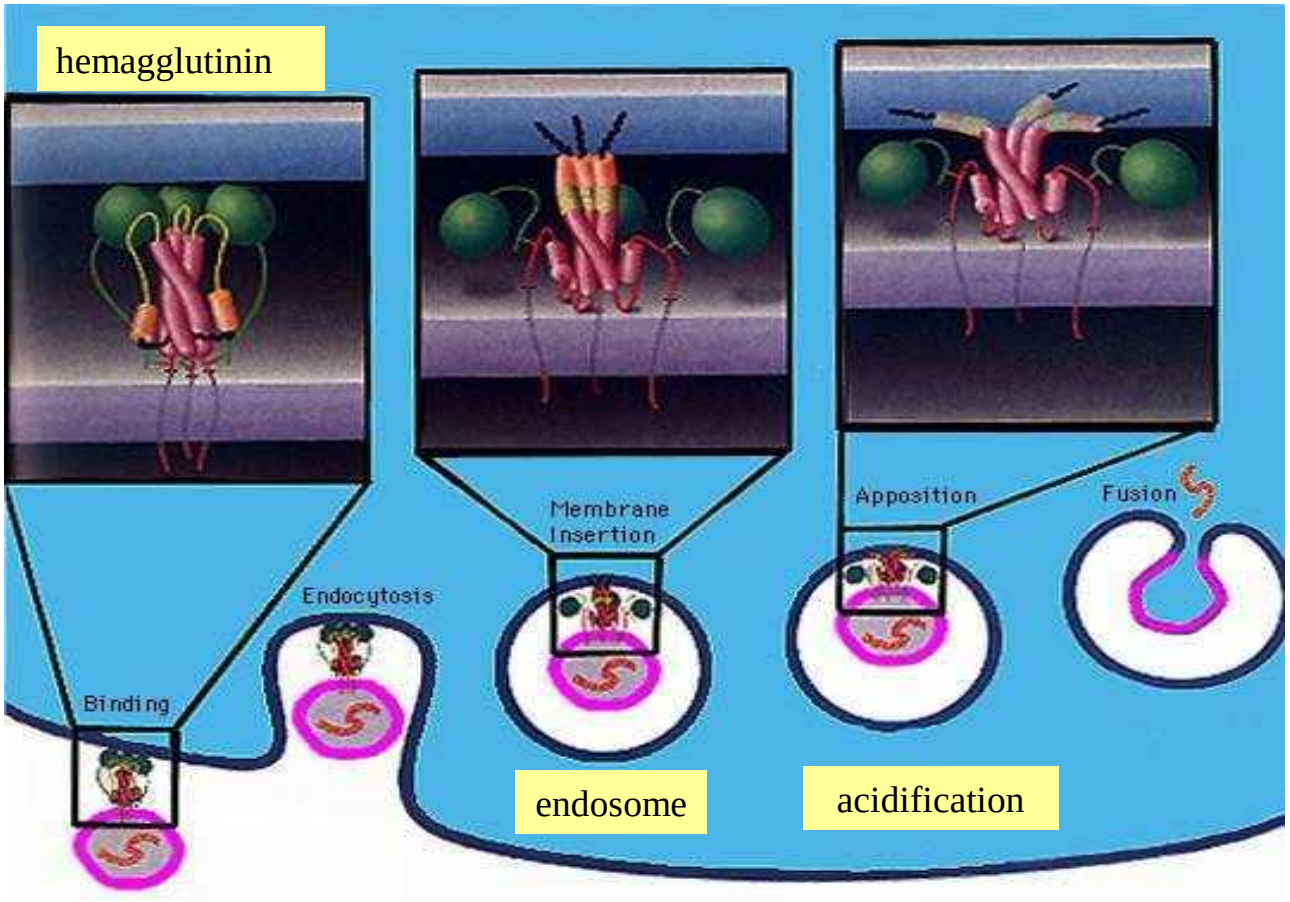


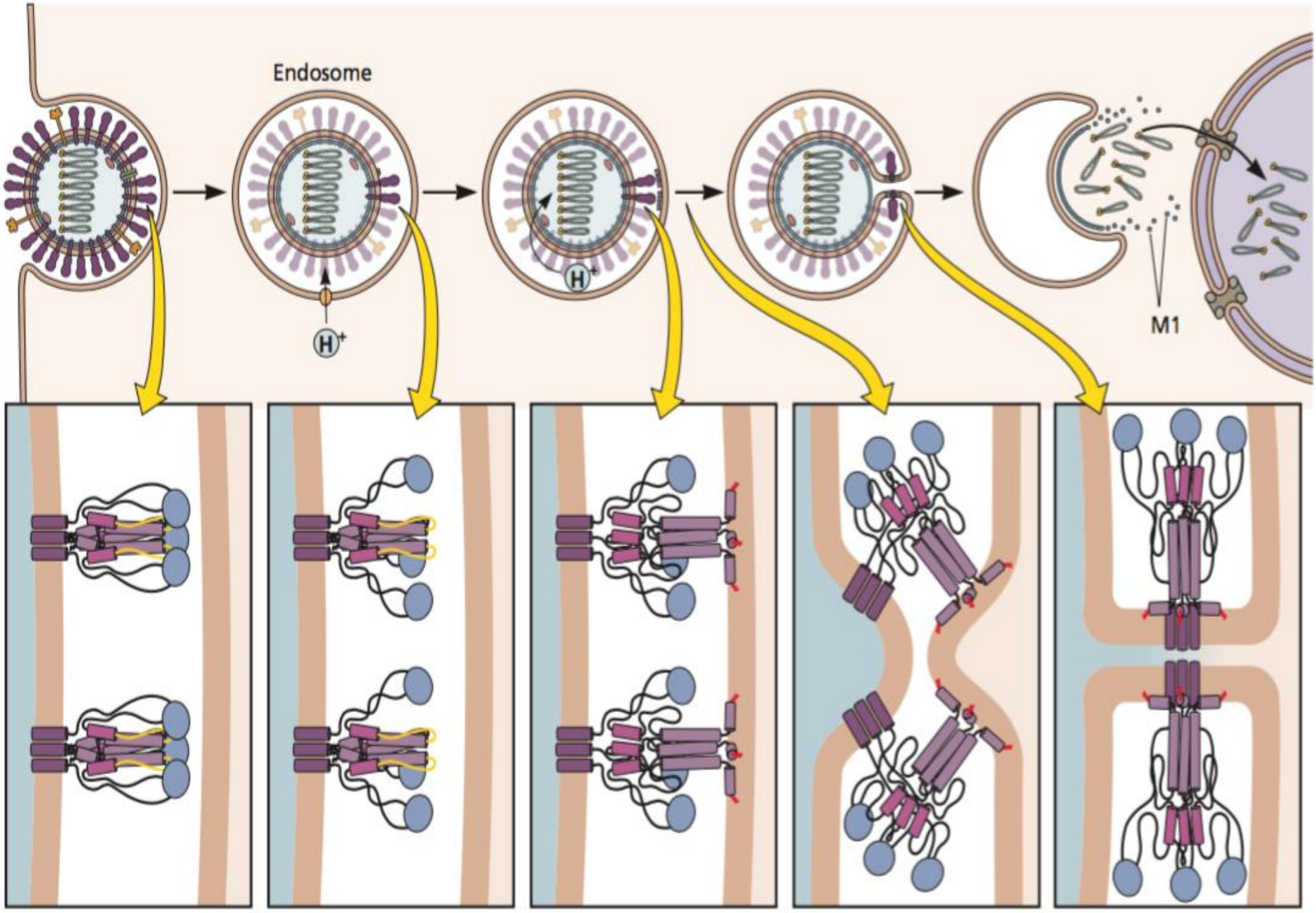
Jiří Nováček et al. PNAS 2016;113:9351-9356

Human rhinovirus entry (HRV, *Picornaviridae*) - ICAM-1 (*intercellular adhesion molecule-1*) receptor, immunoglobulin superfamily.

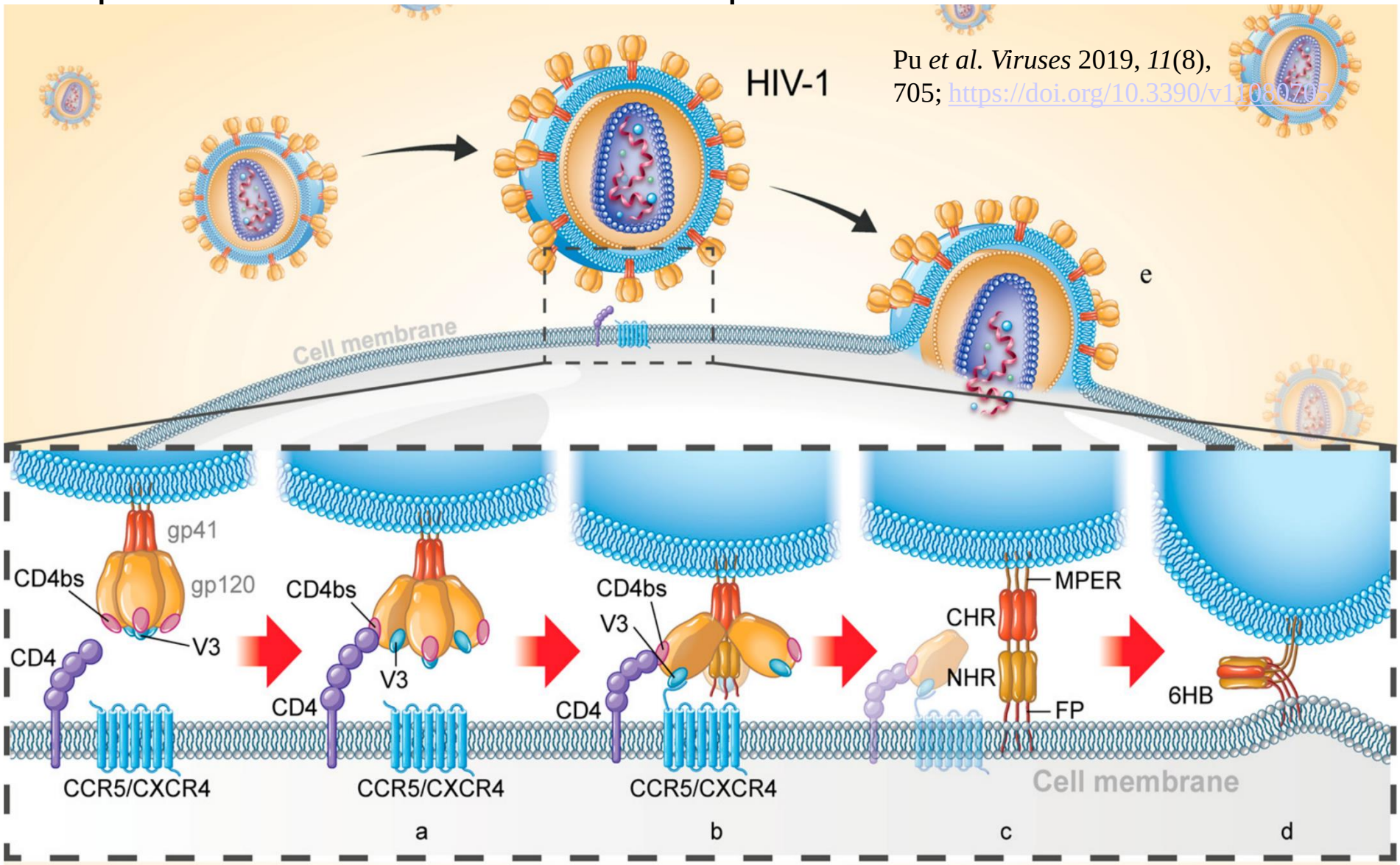


- endocytosis is the most frequent type of entry
  - influenza A

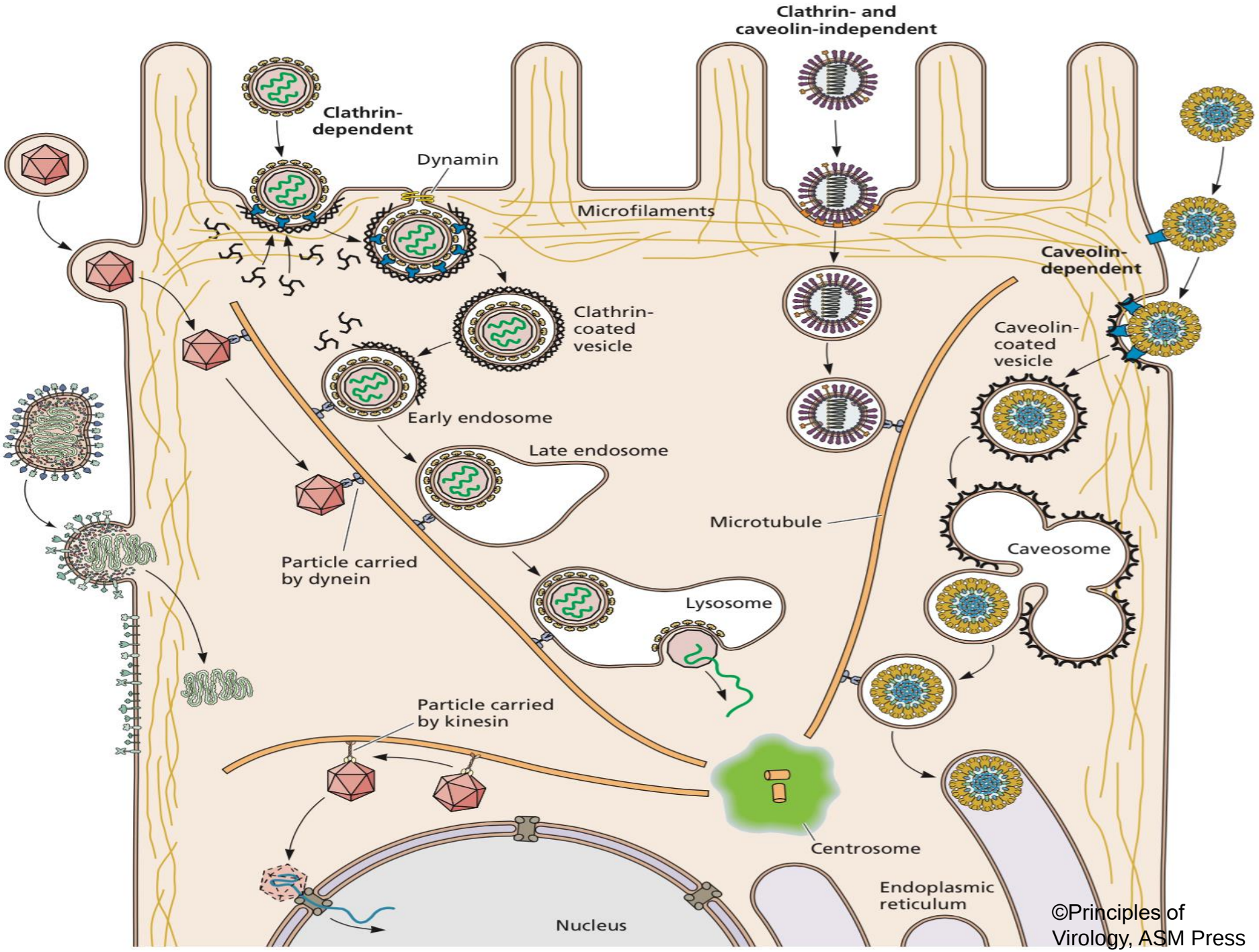




Entry by fusion – enveloped viruses, genome or a whole capsid/nucleocapsid (*core*) enters. HIV-1 receptor is CD4, a chemokine receptor CCR5 or CXCR4 is a coreceptor.



Pu *et al. Viruses* 2019, *11*(8), 705; https://doi.org/10.3390/v11080705



3.-5. Multiplication of the genome and virus proteins

Phages and some animal viruses insert only genome into a cell, most animal viruses enter with nucleocapsid. It needs to be uncoated to start transcription and translation of the genome.

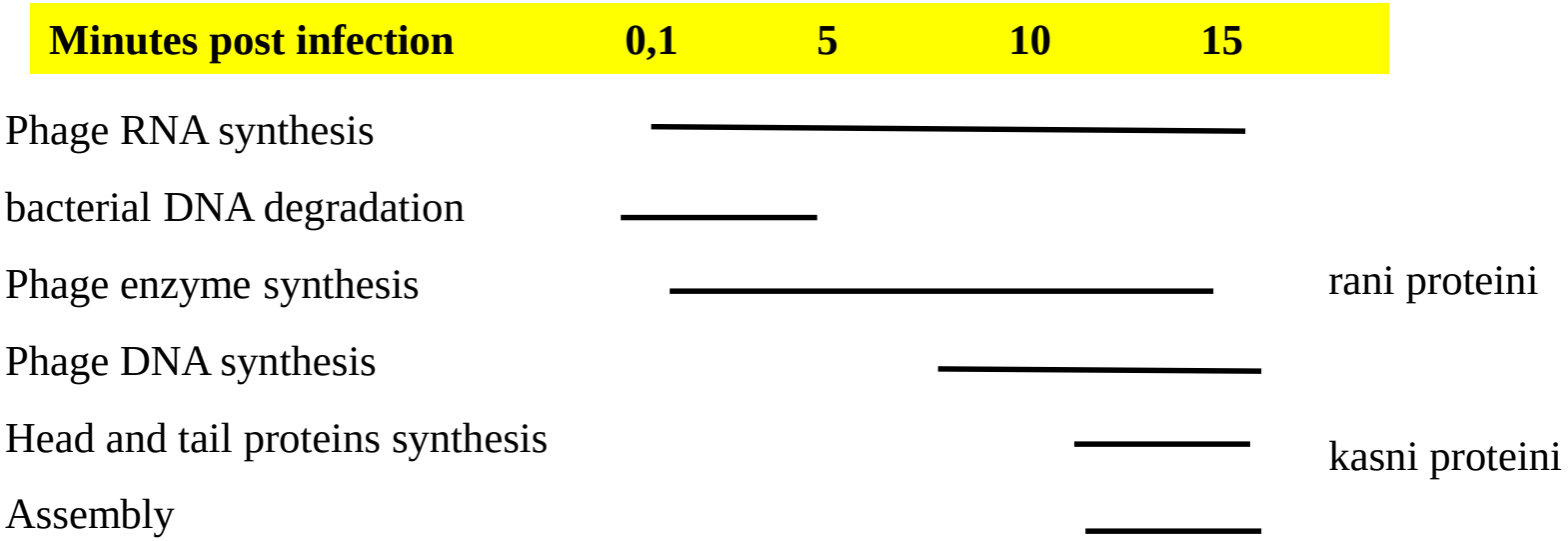
The genome is uncoated and resources of the cell found to do these processes. Where?

Enzymes needed for nucleic acids synthesis: DNA- and RNA-polymerases (which ones?), endonucleases, exonucleases, ligases, topoisomerases...

Most of the viruses discovered before the age of metagenomics change the and organism cell metabolism. Others latently infect their hosts (iceberg effect).

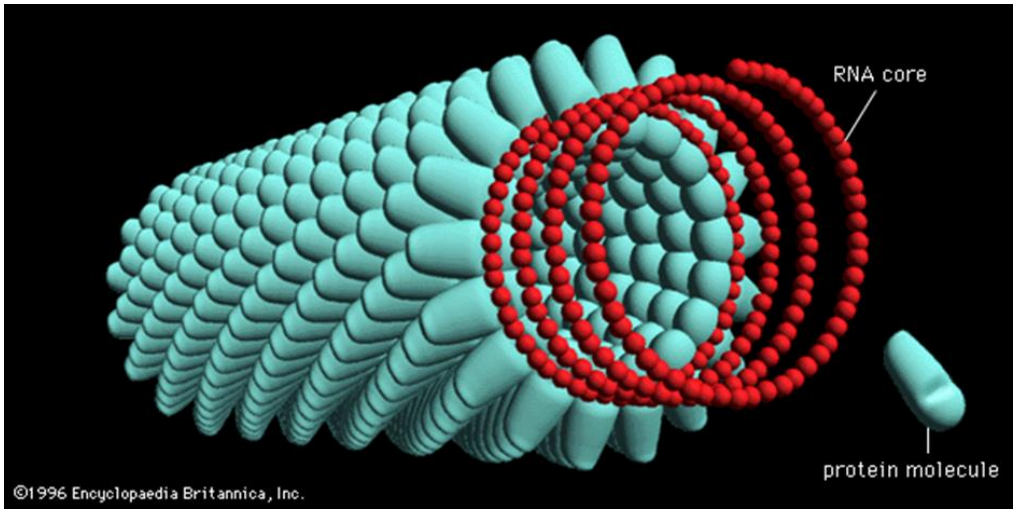
Changes at the level of cellular nucleic acids:

1) Stops or changes host DNA synthesis
2) Changes or disrupts host mRNAs
3) Stops host mRNA synthesis because it changes RNA polymerase (T4)
4) Disintegrates host DNA, phage DNA is tagged and protected (5-methyl cytosine)
5) Changes ribosomes – higher affinity for viral mRNAs
6) Modifies cell tRNAs and makes those better adapted for the virus



6. Assembly (of the virus particles)

Structural components are assembled and basic structure of the virus particle is made. It does not have to be the final one!



The assembly location depends on the virus:

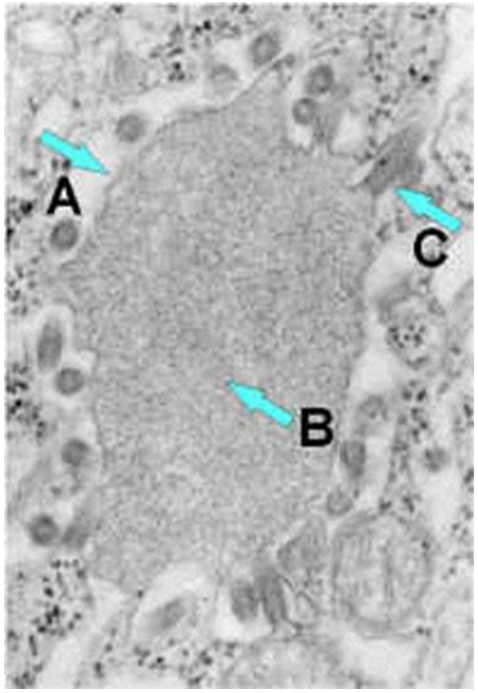
picorna, pox, reoviruses in the cytoplasm,

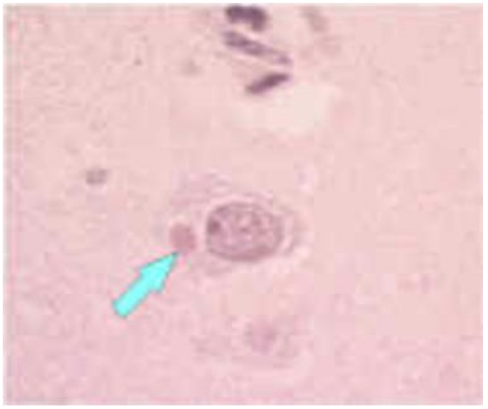
adeno, polyoma, parvo viruses in nucleus.

Cell membrane – after reaching critical level, viral (glyco)proteins are anchored into the membrane in parallel to viral assembly.

Control of the processes is important, both temporal and spatial.

Some viruses compartmentalize the building blocks into a cell – inclusion bodies – e.g. Negri bodies (rabies virus).





Particle formation is a simple process determined by the rules of symmetry and interactions between capsid proteins in some viruses.

In others, stepwise and complex - viral structural proteins, other v. proteins, cell skeletal proteins participate in the process as “scaffolding” but are not part of the virion.

- Maturation – viral particle becomes infectious (virion).

Specific cleavage of capsid proteins and formation of mature products, or conformational changes in the protein during particle constitution.

Picornaviruses - strongly altered antigenicity during maturation.

Condensation of proteins and genomes within the nucleocapsid for many DNA viruses.

Viral proteases may be involved in maturation - very specific peptide bond cleavage reactions.

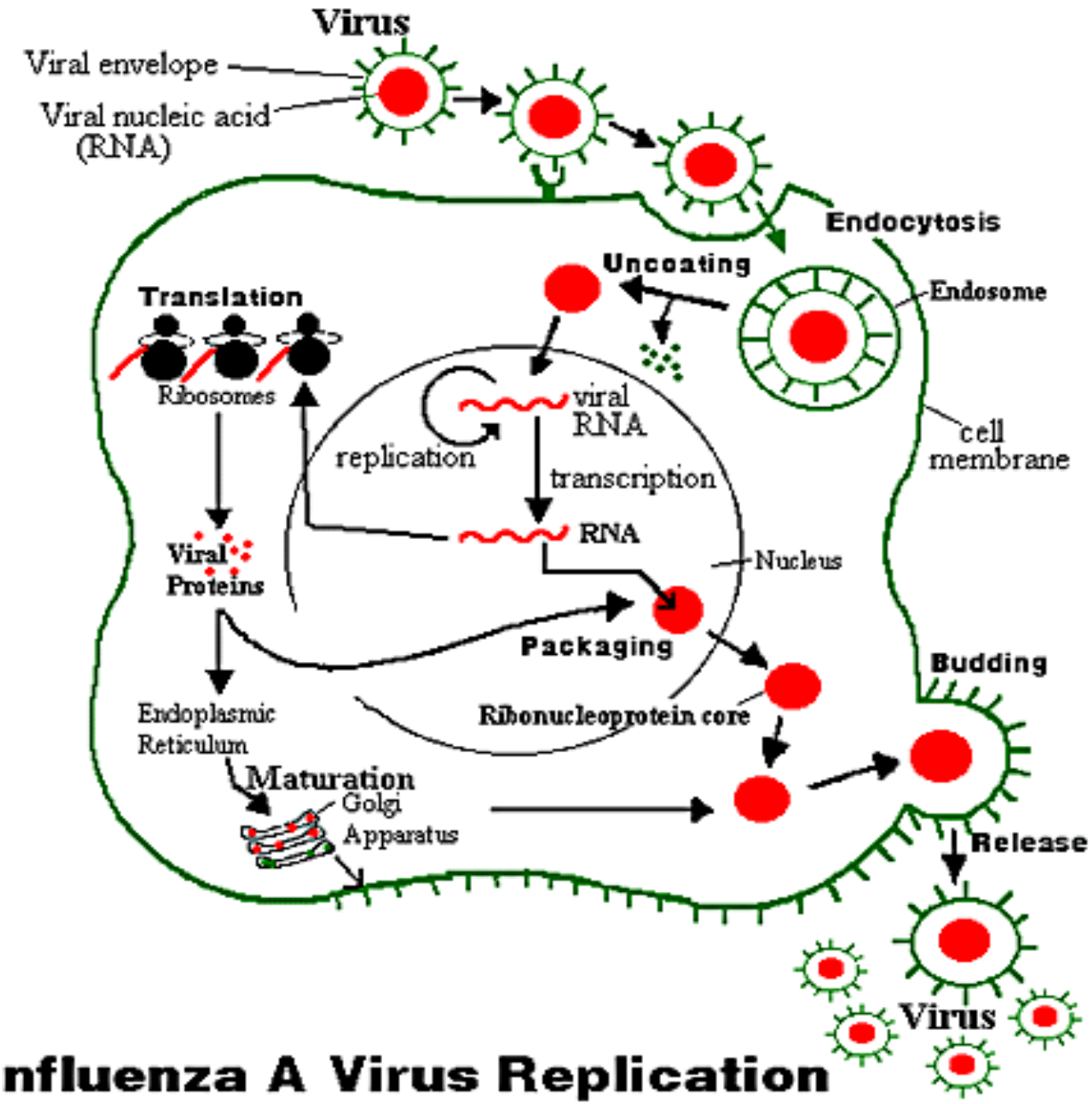
Sometimes cellular enzymes are involved (e.g. furin) or cellular and viral.

7. Exit

For most unenveloped viruses, the exit is lytic (phage lipase, lysozyme; poliovirus), and the envelopes bud through the membrane (retro, toga, ortomyxo, paramyxo, bunya, corona, rhabdo, hepadna; f1 and fd-fagi, as opposed to endocytosis) or into the intracellular structure (tubules, ER vesicles, intercellular junctions) and then exit out of the cell.

Budding can cause cell damage (paramyxo, rhabdo, toga viruses) or not (retroviruses).

For some viruses the regulation of exit is well studied (neuraminidase - IAV), temporal and spatial regulation must be very precise of all later steps in the cycle (assembly, maturation, exit). These phases often overlap.



Influenza A Virus Replication