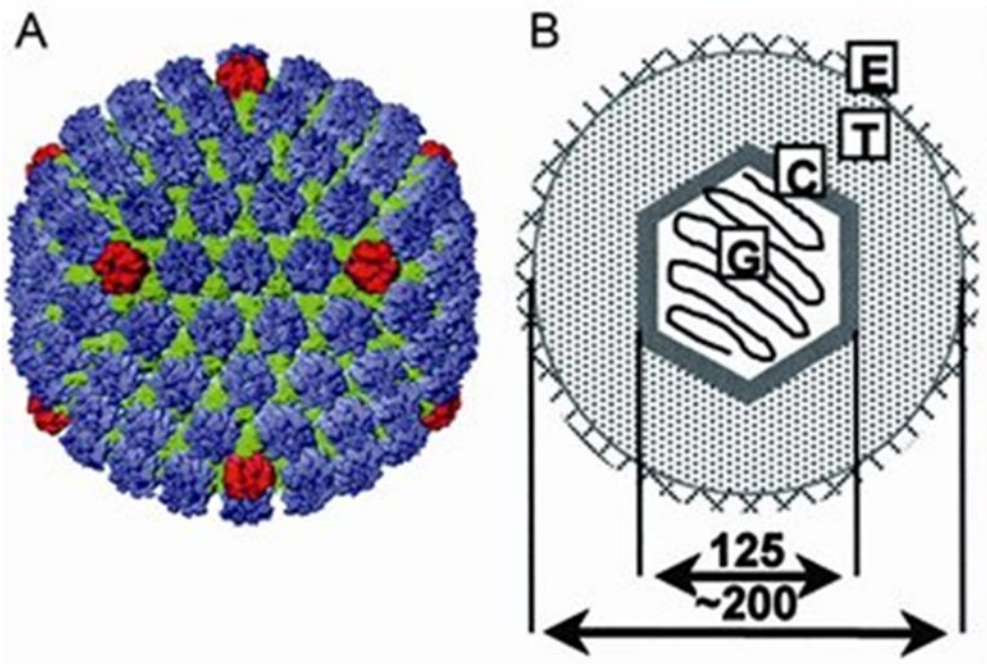
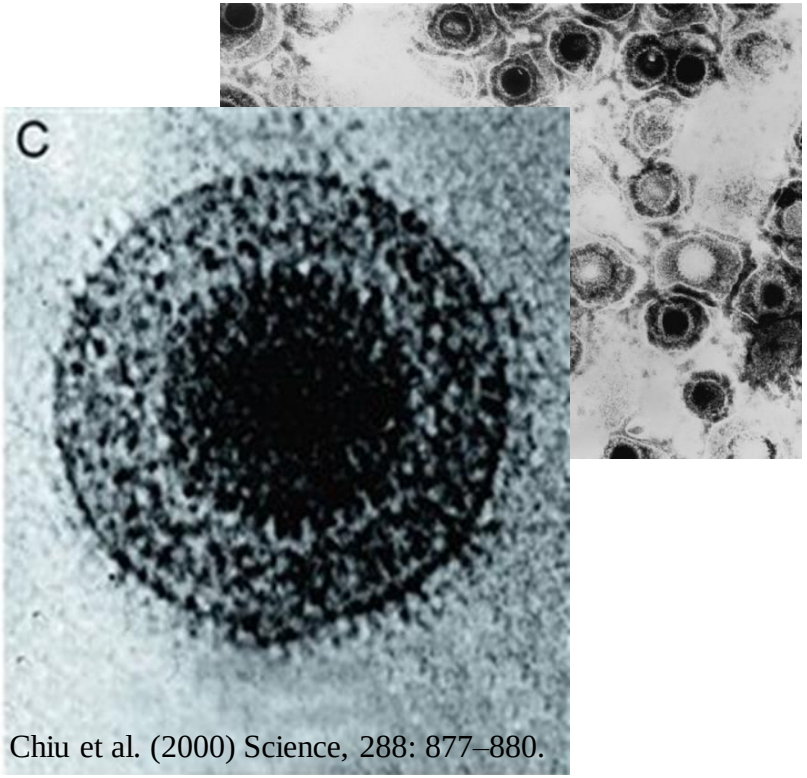
Viruses with dsDNA genomes (2):





Chiu et al. (2000) Science, 288: 877–880.

Order *Herpesvirales*

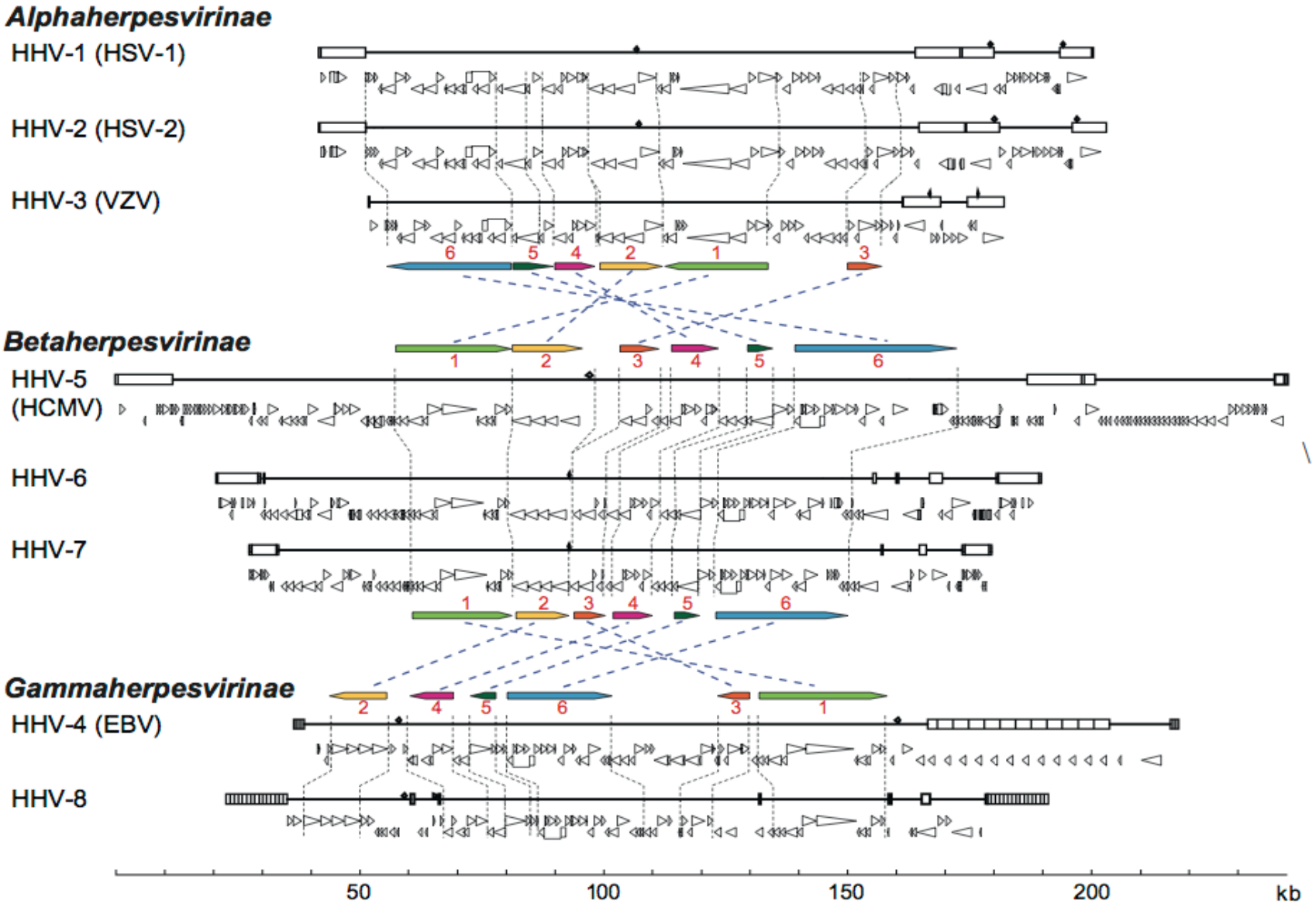
More than 100 viruses of mammals, birds, fishes, reptiles, amphibians and shellfish.

Commonalities: genome type and size, virion type, dual viral cycle (infection types)

Herpesviridae - mammals, birds, reptiles

Family *Herpesviridae* - in mammals, birds and reptiles

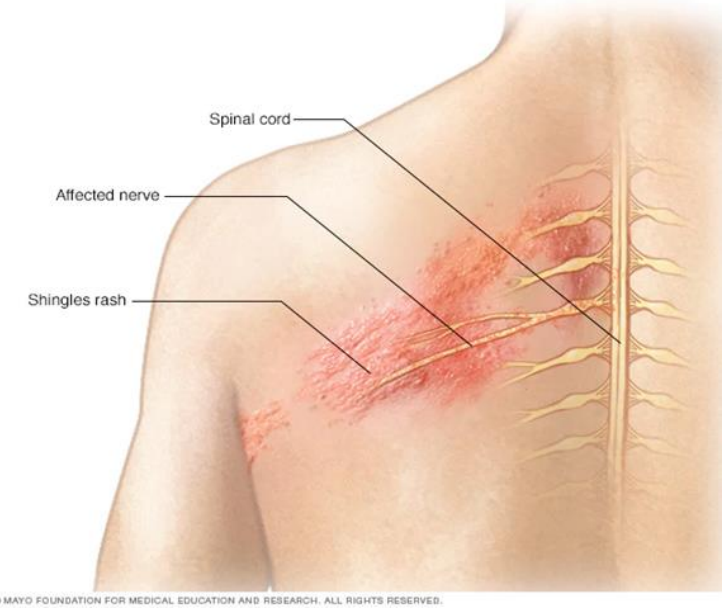
Subfamilies: *α*-, *β*-, *γ*-*herpesvirinae*, 8 human viruses in all three subfamilies.



***α-herpesvirinae:* short lytic cycle, latency in sensory neurons, painful skin symptoms**

•HHV-1 (*Human herpesvirus 1*) = HSV-1 (herpes simplex virus), contact transmission, mucosa, skin, cornea infections (epithelial cells), transport to the neuron nuclei.
Persistent , latent infection, symptoms during productive (acute) infection.
HHV-2 = HSV-2, genital herpes, sexually transmitted, epithelial cells, infant mortality is 54%!
Herpesviruses are neurothropic!

HHV-3 = VZV (varicella-zoster), chickenpox and shingles, aerosol (droplet) transmission usually in childhood, latent in neurons (and T-cells) of head and torso.

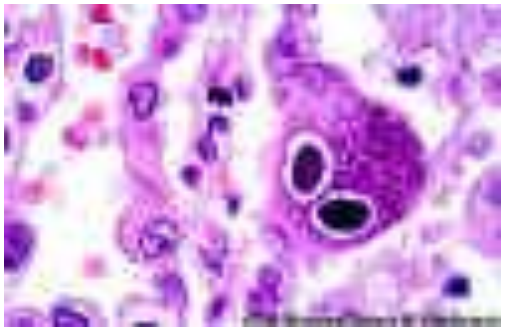


β-herpesvirinae: long cycle, latency in different cell types (mostly white blood cells), enlarged cells

HHV-5 = (h)CMV (human cytomegalovirus) – mils symptoms or asymptomatic infections (10% infectious mononucleosis cases), ubiquitous (90%). Contact transmission and bodily fluids (saliva, urogenital excreta, blood, milk, sperm), fomites, transplantation, transfusion).

Replication in lymphocytes, latency in bone marrow (myeloid progenitor cells to be differentiated to monocyte).

Congenital hCMV) in fetuses and newborns (brain, liver, spleen damage, mental impairment, deafness, death), immunocompromised patients:
transplanted (the most important virus tested) and AIDS (retinitis, colitis).



http://pathmicro.med.sc.edu/virol/herpes.htm

HHV-7 (from CD4+ T-cell culture of a healthy person), transmission by saliva, urogenital excreta.

β-herpesvirinae: long cycle, latency in different cell types (mostly white blood cells), enlarged cells

HHV-6, (HHV6A i 6B) children – *exanthem subitum*, (*roseola infantum*, *6th disease*),

All children usually infected 6 m.-2 y., mild respiratory disease, high fever (40°C) 3-4 days, rash on torso afterwards.

Latency in CNS, macrophages, monocytes, probably in T-cells, reactivation (short fever).

Saliva and contact transmission, episome is integrated in telomeres.

Chronic fatigue syndrome?

γ-herpesvirinae: latency in lymphocytes, oncogenic

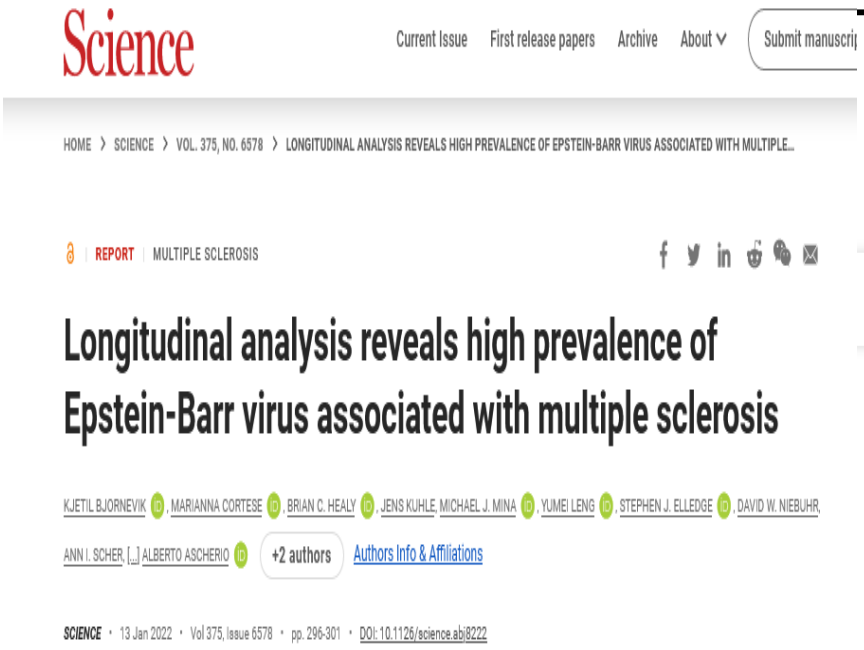
HHV-4 = EBV (Epstein-Barr virus) – mononucleosis (90%, a kissing dosease), transmission from saliva to epithelial cells and mostly B-cells (latency), some to T-cells, tonsilles and on to lymphatic tissue.
Primary acute infection 4-8 weeks, various symptoms, mostly not severe.
Burkitt's limphoma (endemic, sporadic, AIDS), nasopharynx carcinoma, sometimes Hodgkin limphoma, non-Hodgkin limfom in AIDS, post-transplant lymphoproliferative disease.

HHV-8 (Kaposi sarcoma – KSHV, isolated in 1994 from tumor tissue), lymphocytes and other host cells.

www.nhs.uk/conditions/kaposis-sarcoma/

EBV and multiple sclerosis (MS) link!

Seminar?



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HOME › SCIENCE › VOL. 375, NO. 6578 › LONGITUDINAL ANALYSIS REVEALS HIGH PREVALENCE OF EPSTEIN-BARR VIRUS ASSOCIATED WITH MULTIPLE...

REPORT | MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

KJETIL BJORNEVIK, MARIANNA CORTESE, BRIAN C. HEALY, JENS KUHLE, MICHAEL J. MINA, YUMEI LENG, STEPHEN J. ELLEDGE, DAVID W. NIEBUHR, ANN I. SCHER, [...] ALBERTO ASCHERIO +2 authors Authors Info & Affiliations

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Article | Published: 24 January 2022

Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM

Clonally expanded B cells in multiple sclerosis bind EBV EBNA1 and GlialCAM

27k Accesses | 10 Citations | 887 Altmetric | Metrics

Abstract

Multiple sclerosis (MS) is a heterogenous autoimmune disease in which autoreactive lymphocytes attack the myelin sheath of the central nervous system. B lymphocytes in the cerebrospinal fluid (CSF) of patients with MS contribute to inflammation and secrete oligoclonal immunoglobulins[1,2]. Epstein–Barr virus (EBV) infection has been epidemiologically linked to MS, but its pathological role remains unclear[3]. Here we demonstrate high-affinity molecular mimicry between the EBV transcription factor EBV nuclear antigen 1 (EBNA1) and the central nervous system protein glial cell adhesion molecule (GlialCAM) and provide structural and in vivo functional evidence for its relevance. A cross-reactive CSF-derived antibody was initially identified by single-cell sequencing of the paired-chain B cell repertoire of MS blood and CSF, followed by protein microarray-based testing of recombinantly expressed CSF-derived antibodies against MS-associated viruses. Sequence analysis, affinity measurements and the crystal structure of the EBNA1–peptide epitope in complex with the autoreactive Fab fragment enabled tracking of the development of the naive EBNA1-restricted antibody to a mature EBNA1–GlialCAM cross-reactive antibody. Molecular mimicry is facilitated by a post-translational modification of GlialCAM. EBNA1 immunization exacerbates disease in a mouse model of MS, and anti-EBNA1 and anti-GlialCAM antibodies are prevalent in patients with MS. Our results provide a mechanistic link for the association between MS and EBV and could guide the development of new MS therapies.

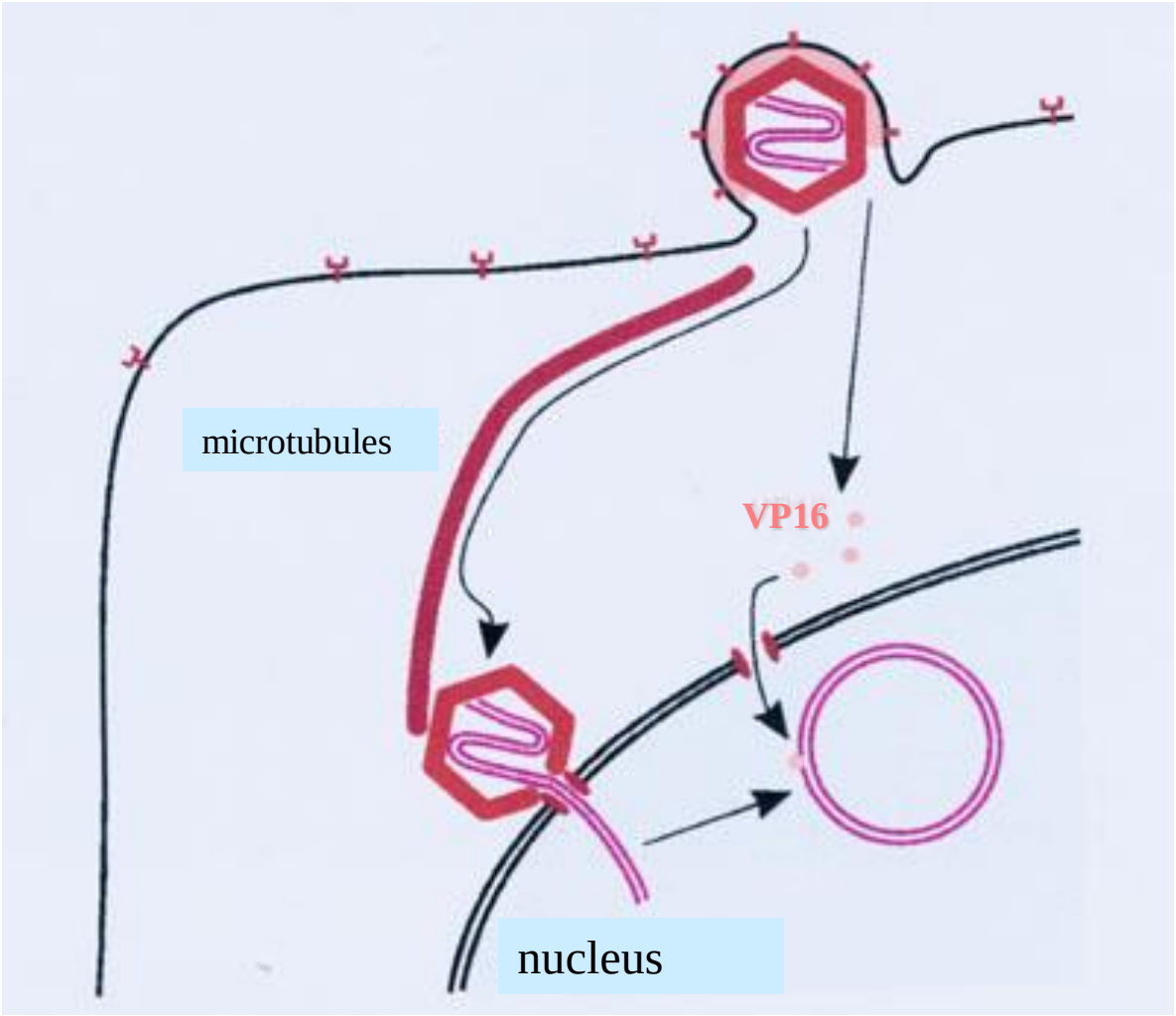
TWiV 869: Epstein-Barr virus and MS, a perfect storm

https://youtu.be/zqtI36oNWtI

HHV-1

virion

genome



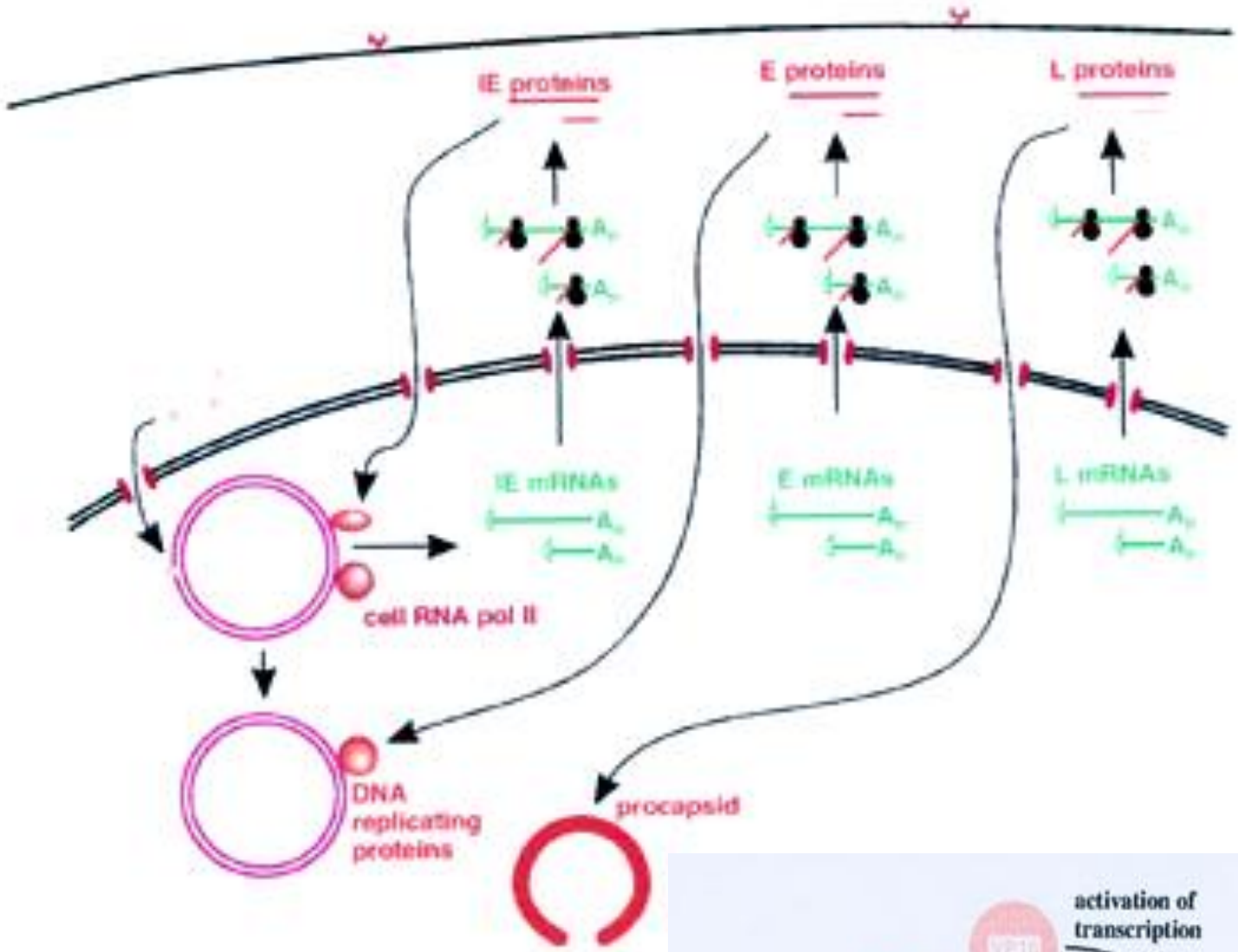
Adapted from Carter & Saunders, 2007.

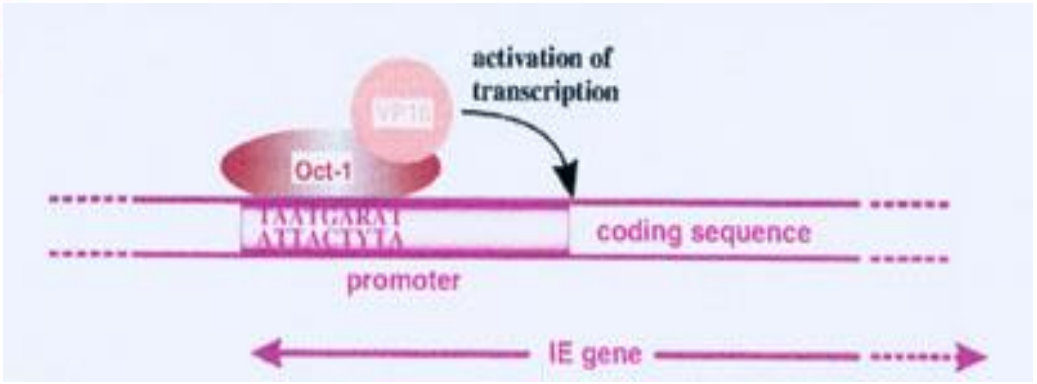
Linear genome circularizes!

Encodes about 70 proteins.

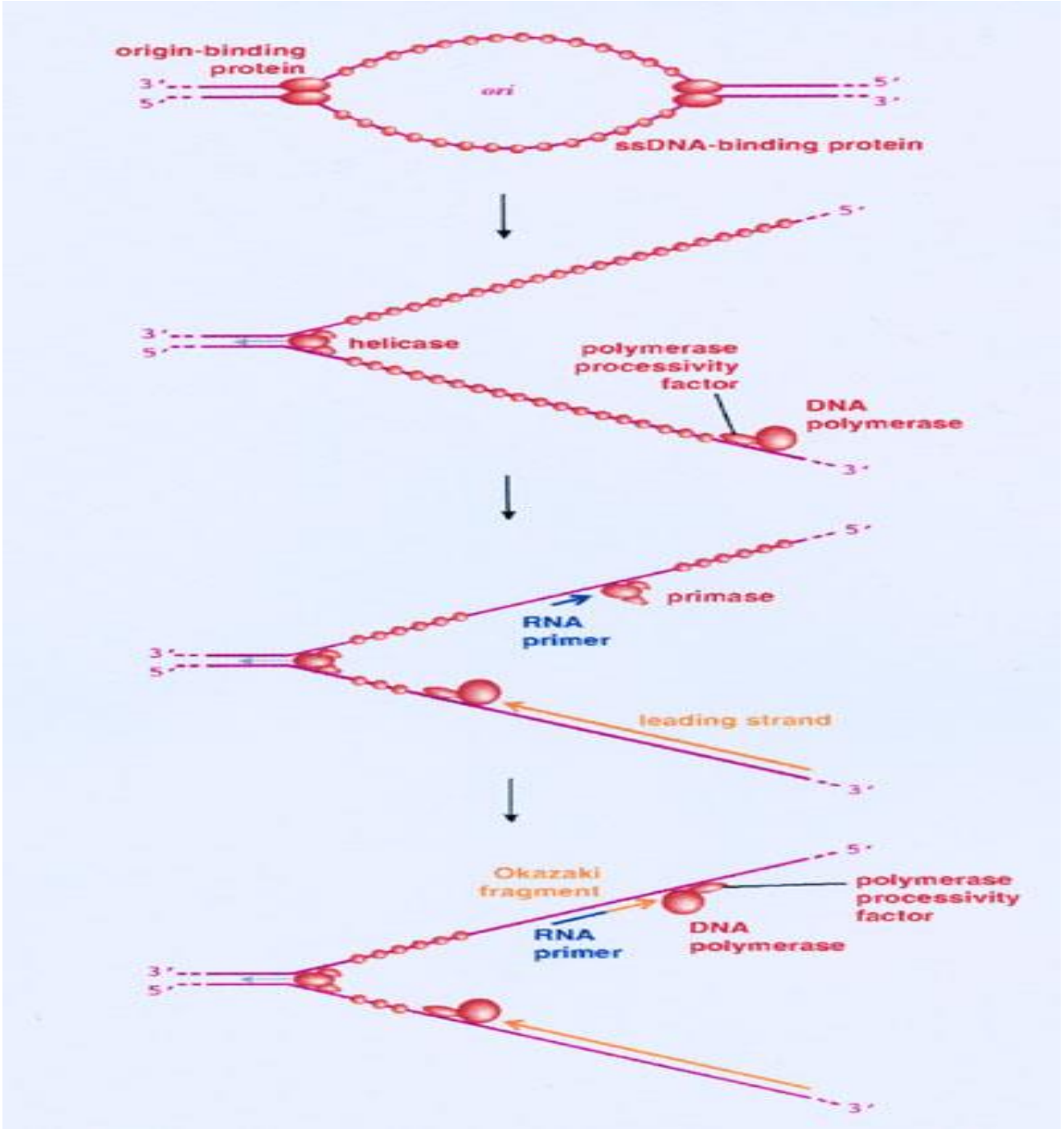
Virion proteins:

- tegument – min. 15 proteins (VP16) + viral mRNAs
- (nucleo)capsid - VP5
- envelope with at least 12 glycoproteins (gB, gC, gD)





Carter & Saunders, 2007.



θ – replication

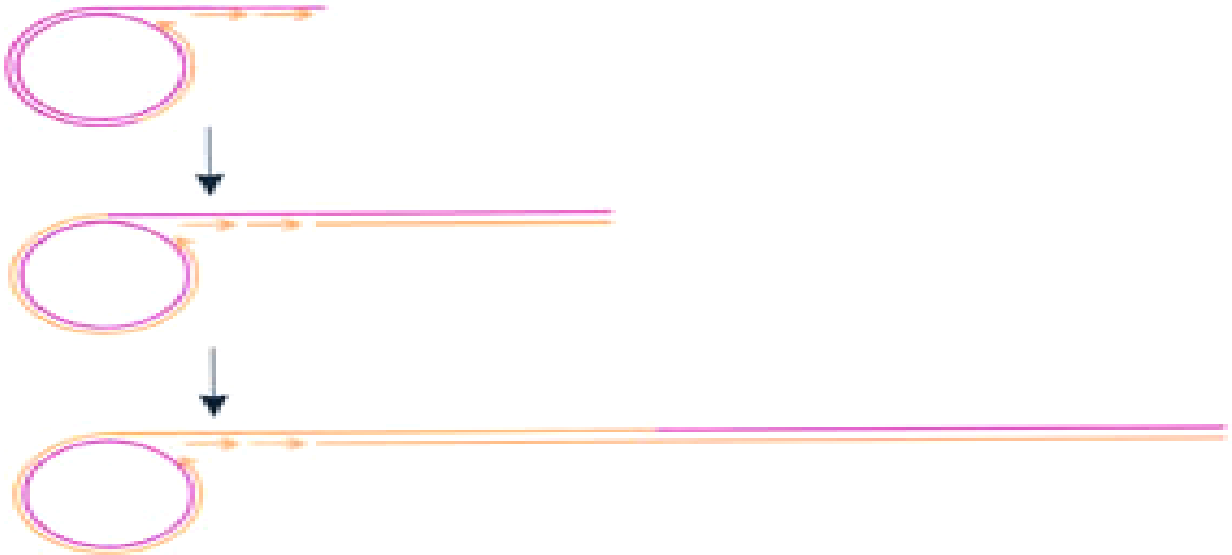
- proteins bind to 1/3 origins of replication.

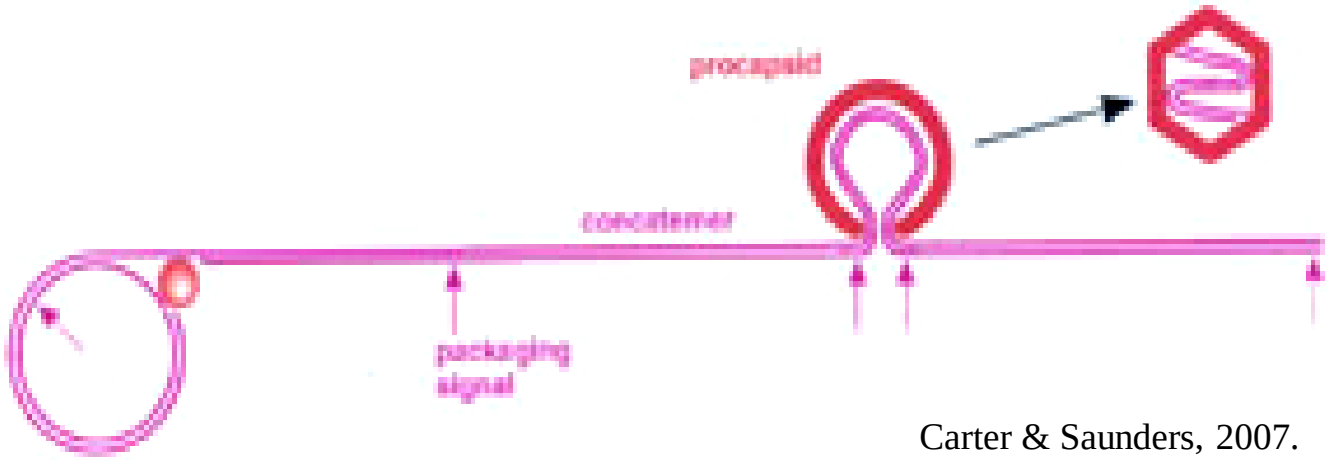
-seven E proteins essential

Carter & Saunders, 2007.

Strauss & Strauss, 2002.

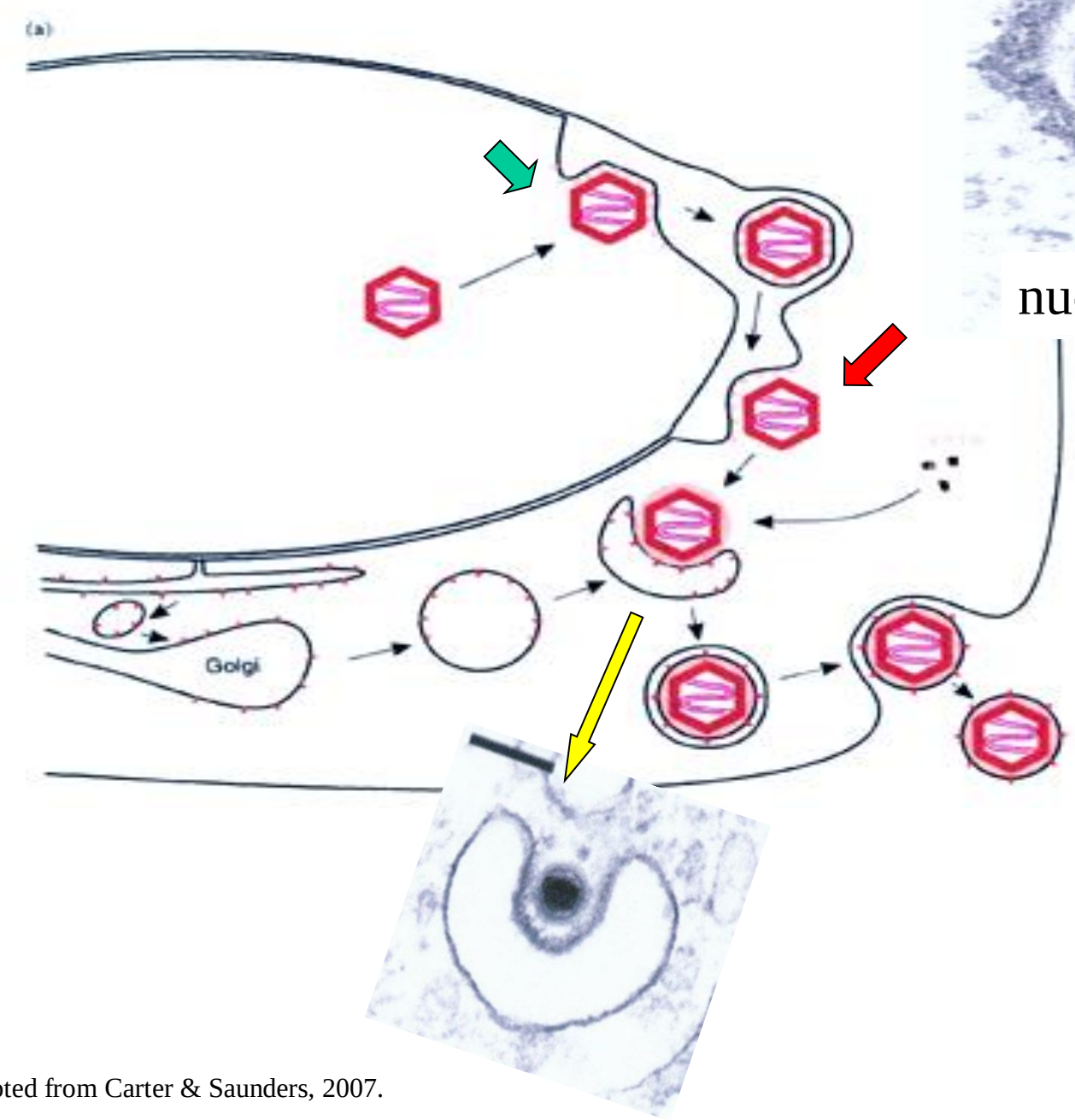
σ - replication

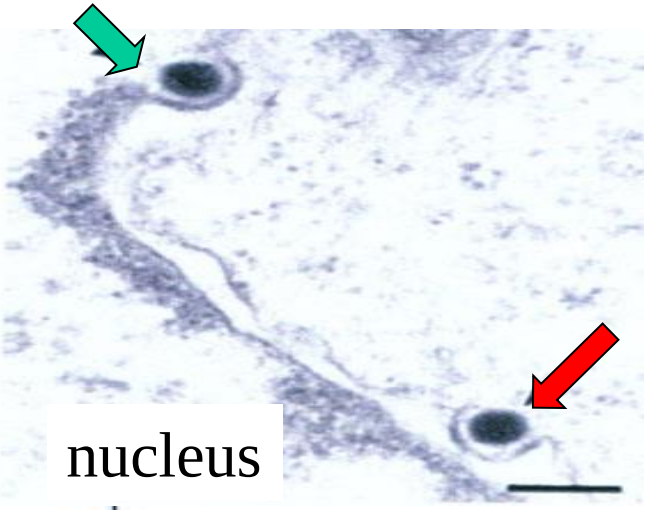




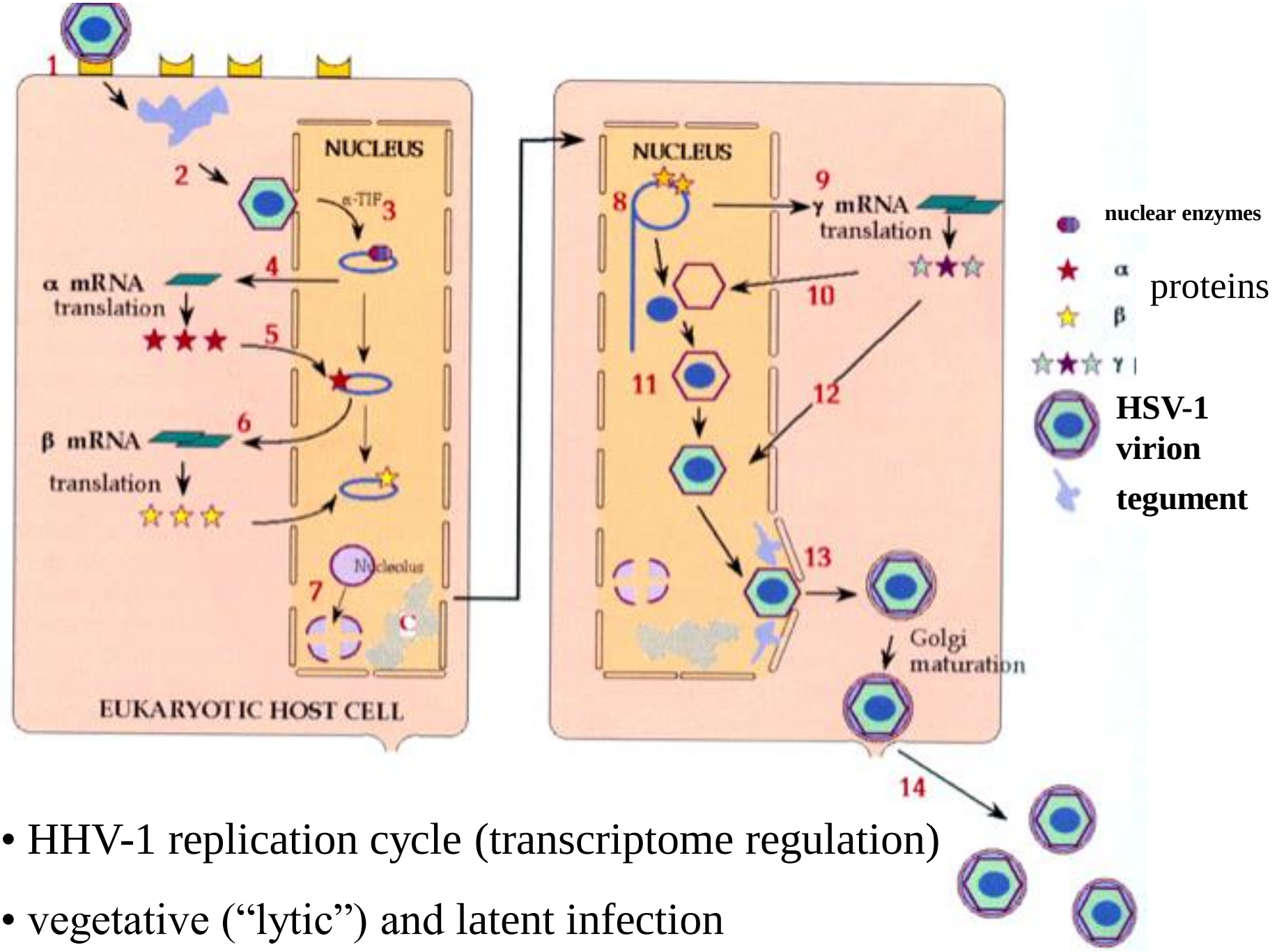
Carter & Saunders, 2007.

HHV-1 exit





Adapted from Carter & Saunders, 2007.



- HHV-1 replication cycle (transcriptome regulation)
- vegetative ("lytic") and latent infection

Strauss & Strauss, 2002.

https://www.bing.com/videos/riverview/relatedvideo?&q=HSV+Latency+Cycle+Animation&&mid=C5885FA91304ADADB362C5885FA91304ADADB362&&FORM=VRDGAR

How does a herpesvirus maintains latency?

HHV LATs – Latency Associated Transcripts

DNA HHV-1 genome region called Latency Associated Transcript Region is in the terminal repeats.

A set of micro RNAs (miRNAs) important for latency is also transcribed from the same locus.

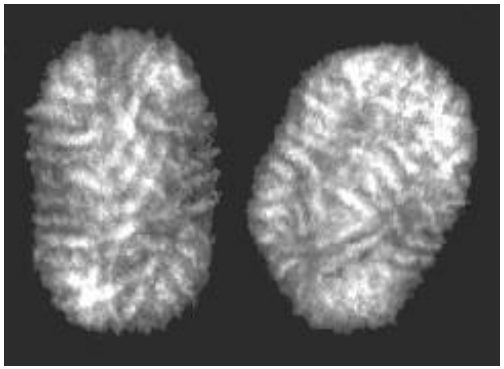
Farrell et al. 1991. Herpes simplex virus latency-associated transcript is a stable intron. Proceedings of the National Academy of Science (USA) 88: 790–794.

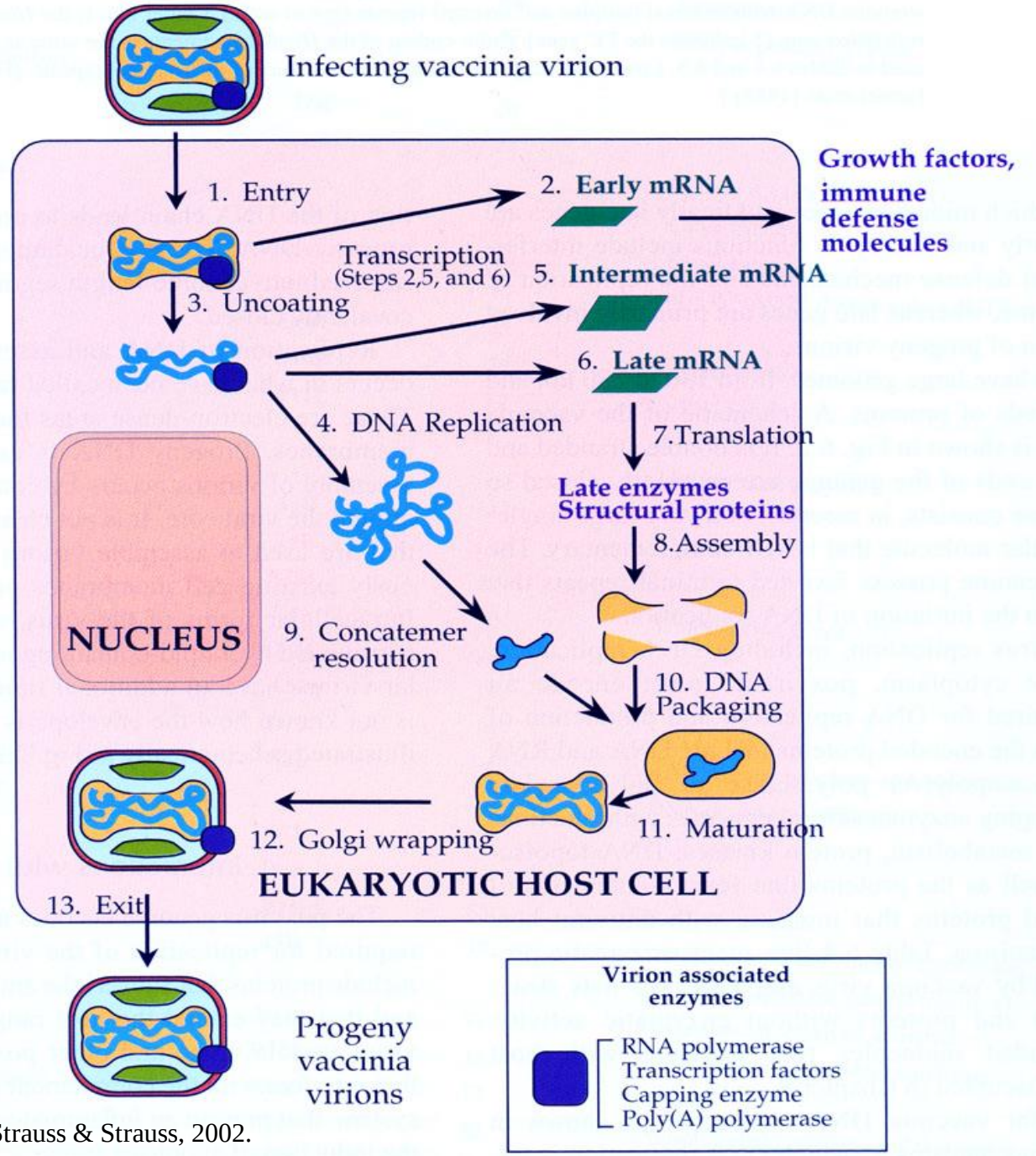
Phelan D, Barrozo ER, Bloom DC. 2017. HSV1 latent transcription and non-coding RNA: a critical retrospective. J Neuroimmunol 308:65–101. https://doi.org/10.1016/j.jneuroim.2017.03.002.

Singh N, Tscharke DC. 2020. Herpes simplex virus latency is noisier the closer we look. J Virol 94:e01701-19. https://doi.org/10.1128/JVI.01701-19.

Family	Subfamily	Genus	Species (virus)
Poxviridae			
	Chordopoxvirinae	*Avipoxvirus*	fowlpox
		Capripoxvirus	sheeppox
		Leporipoxvirus	myxoma
		Molluscipoxvirus	*Molluscum contagiosum*
		Orthopoxvirus	vaccinia
			variola (major, minor)
		Parapoxvirus	orf,
			pseudocowpox (pseudovaccinia)
		Suipoxvirus	swinepox
		Yatapoxvirus	Yaba monkey tumorvirus
			Tanapox monkey virus
	Entomopoxvirinae	*Entomopoxvirus A*	*Melolontha melolontha* entomopoxvirus
		Entomopoxvirus B	*Amsacta moorei* entomopoxvirus
		Entomopoxvirus C	*Chironomus luridus* entomopoxvirus

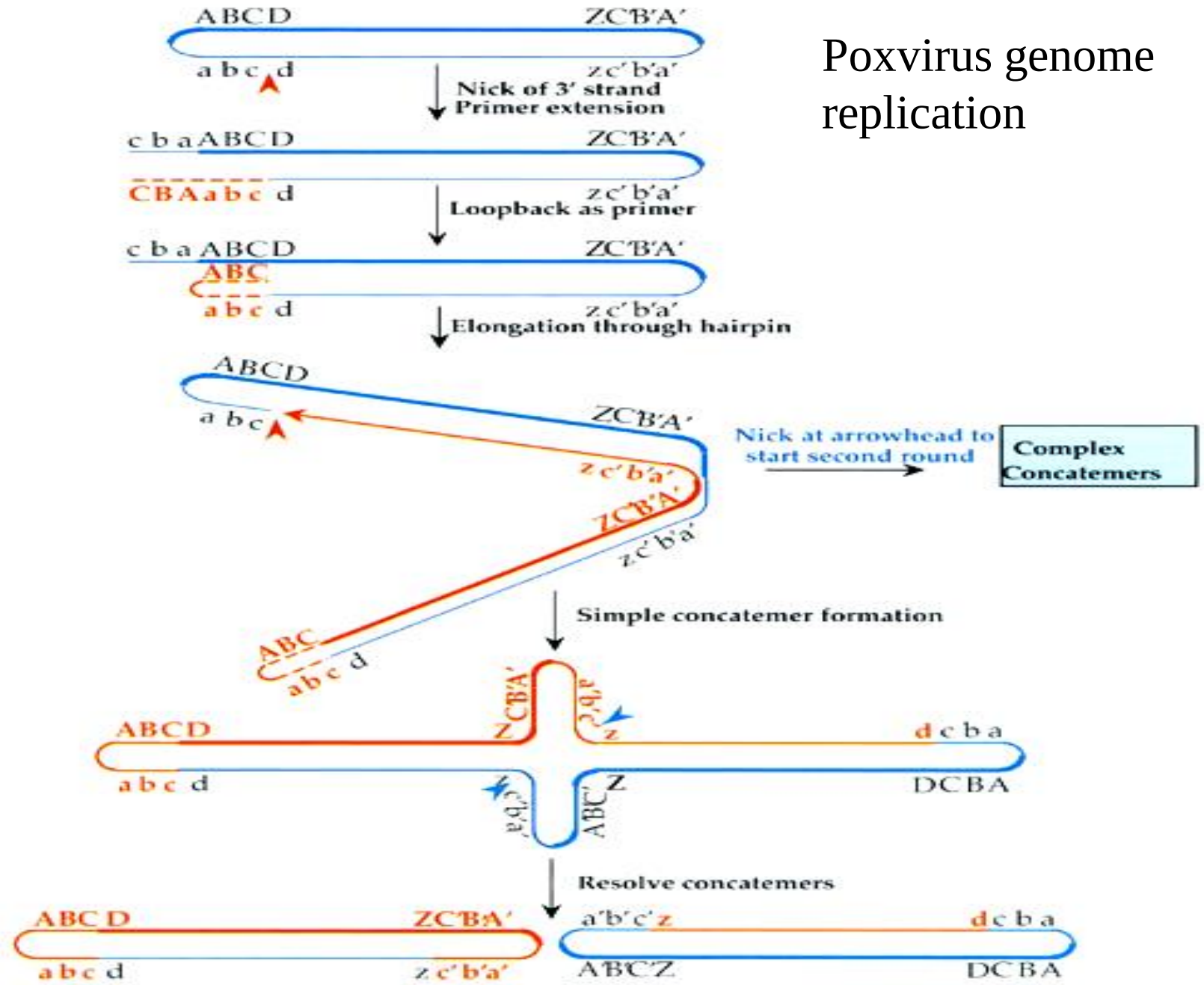
Linear dsDNA-genome with covalently closed ends , 130-300 kbp. More than 200 genes, about 100 proteins, complex strucutre, complete cycle in the **cytoplasm**.





Strauss & Strauss, 2002.

Poxvirus genome replication



Strauss & Strauss, 2002.

Baculoviridae – 90-160 kbp genome, big but not in the NCLDV group in literature, may be a seminar topic.

Main features for viruses with big dsDNA genomes :

•complex,

•genes in both DNA strands,

•linear genomes or linearn that can circularize (Herpes and Pox)

•not found in plant hosts,

•may cause tumors,

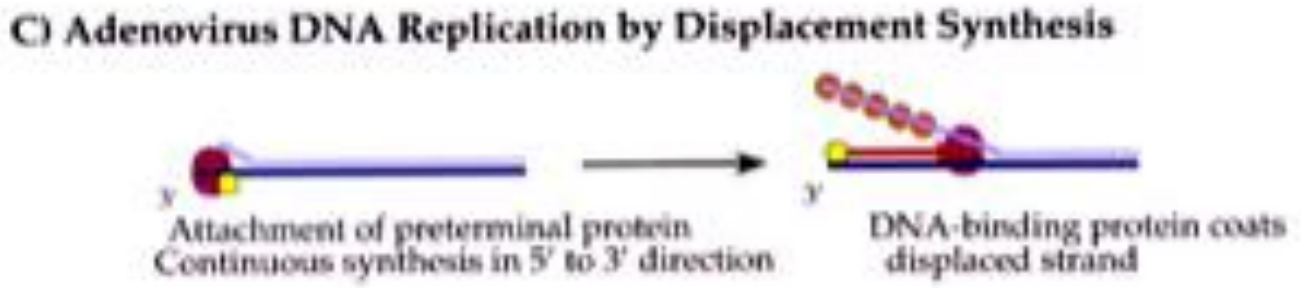
•important cloning vectors,

•important in gene therapy.

Adenoviridae

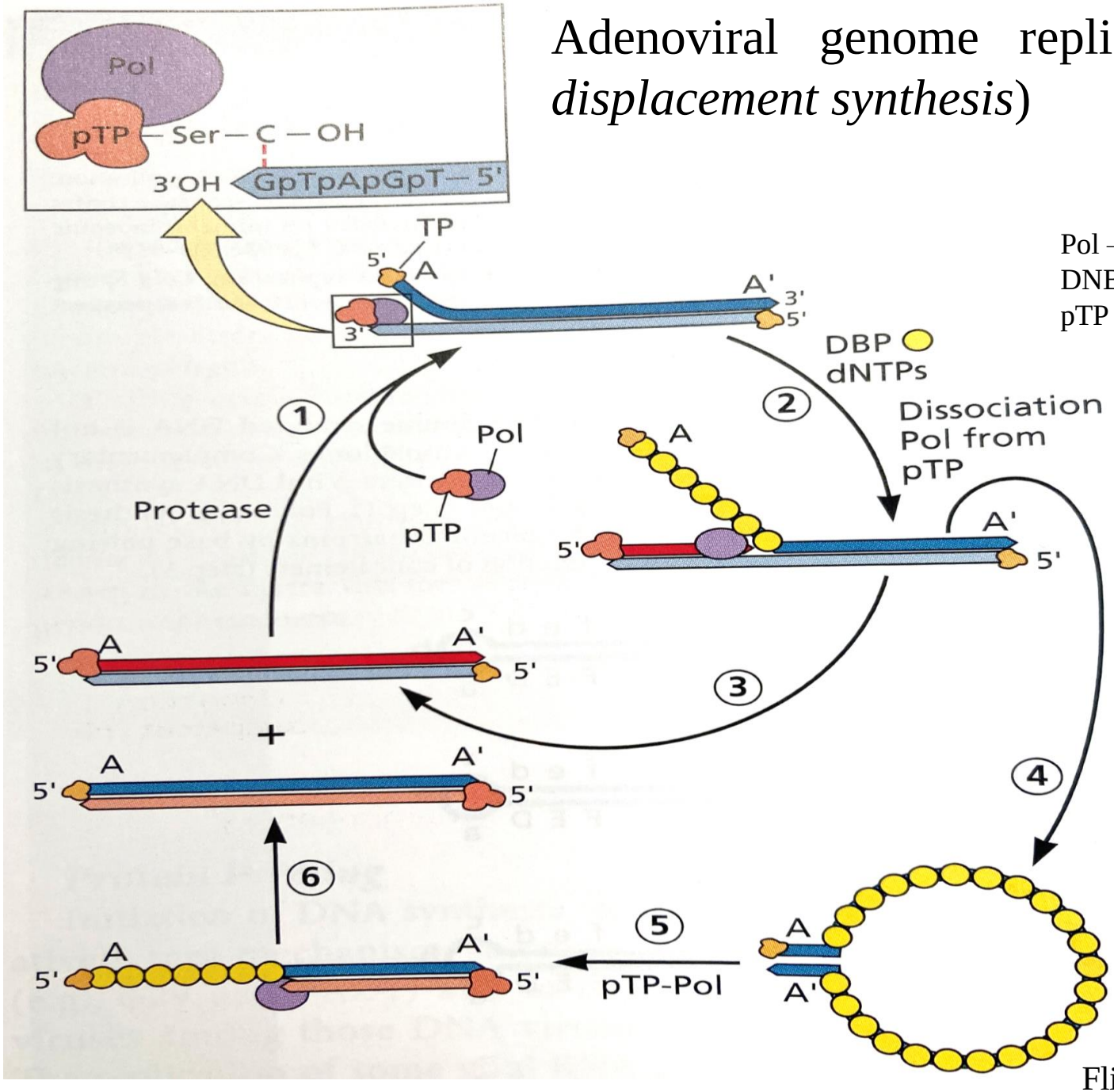
70-100 nm, preterminal protein - ⬭ primer for DNA synthesis .

Genome – linear dsDNA, 24-45 kbp



Strauss & Strauss, 2002.

Adenoviral genome replication (*strand displacement synthesis*)

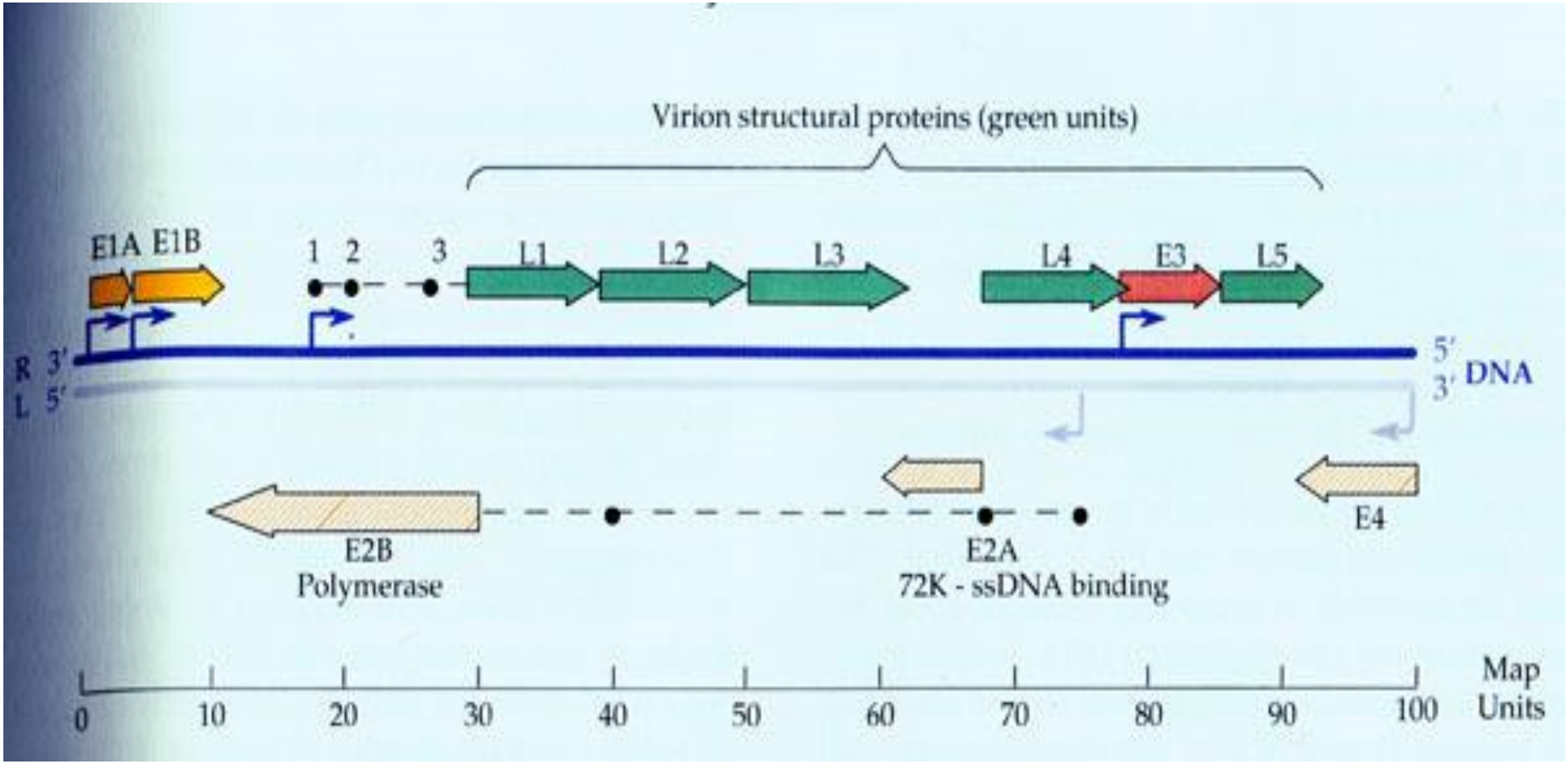


Pol – adenoviral DNApol
DNB – DNA binding protein
pTP – preterminal protein

Flint *et al*. 4th ed., 2015

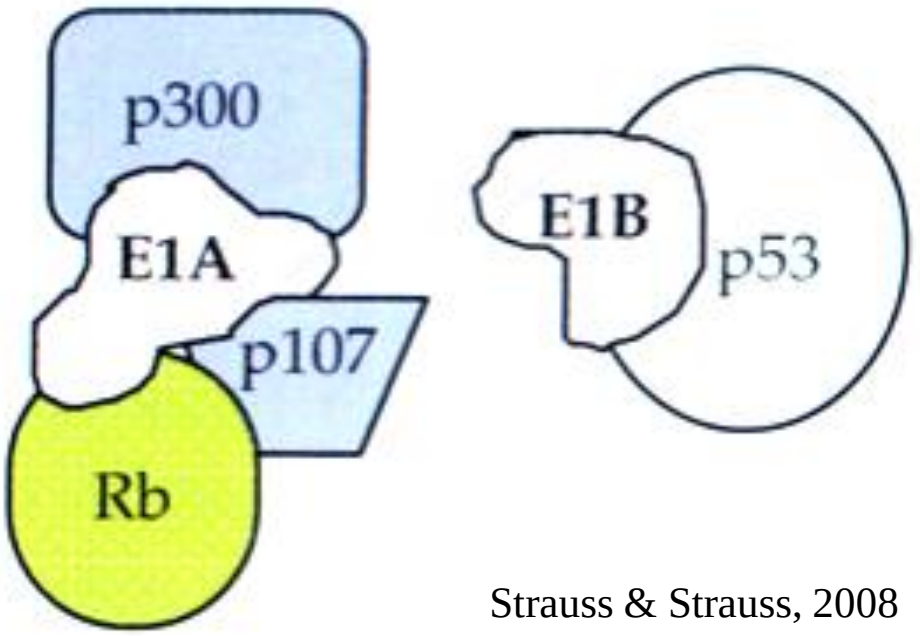
Human adenovirus type 2 – genome organization and transcription

(36 kbp)



Strauss & Strauss, 2008

Adenoviral oncogenic proteins (E1A, E1B) – interaction with cell proteins, stimulate S phase entry – ideal conditions for viral genome replication.



Strauss & Strauss, 2008

Protein Rb (retinoblastoma – optical nerve tumor) – stops cell growth (hyperphosphorylated, bound to E2F) in G1 phase, cells that are not ready wait in S phase. Rb phosphorylation, E2F dissociates and activates gene transcription for entry into the S phase.

p53 - anti-oncogenic protein, tumor suppressor, activates gene transcription that halt cell cycle progression, regulates cell cycle (pause in G1/S), DNA repair and apoptosis.