THE HUMAN HERPESVIRUSES

General features:

- Architecture
- Genome organisation
- Replication
- Nomenclature and classification
- Biological properties
- Latency

Features of specific herpesviruses

- Epidemiology
- Pathogenesis
- Clinical features
- Diagnosis

INTRODUCTION TO THE FAMILY *HERPESVIRIDAE*

GENERAL CHARACTERISTICS

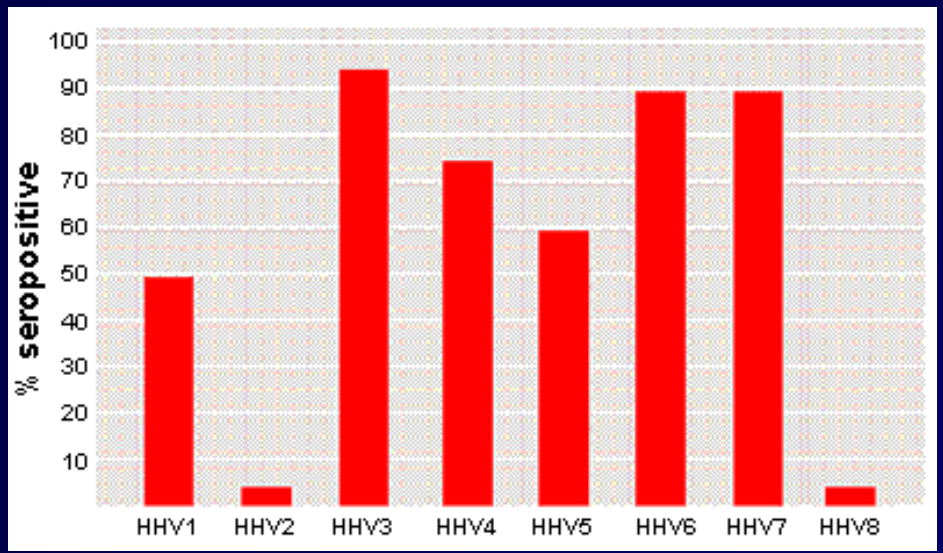
- One of the largest human viruses
- HV infections have been recognised since ancient times
- "*herpein*" = "to creep" in ancient Greek (Hippocrates)
- Herpesviruses are highly disseminated in nature
- Highly species specific
- ~100 Herpesviruses have been isolated, at least one for most animal species which have been investigated. To date, there are 8 known human Herpesviruses.

THE HUMAN HERPESVIRUSES

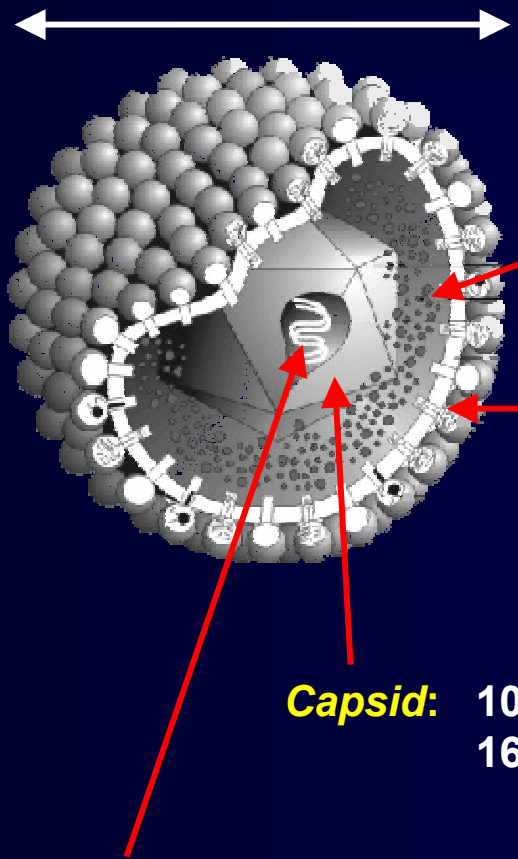
Human herpesvirus type 1	(Herpes simplex virus -1)
Human herpesvirus type 2	(Herpes simplex virus -2)
Human herpesvirus type 3	(Varricella zoster virus)
Human herpesvirus type 4	(Epstein-Barr virus)
Human herpesvirus type 5	(Cytomegalovirus)
Human herpesvirus type 6	
Human herpesvirus type 7	
Human herpesvirus type 8	

Herpes B virus

- Herpes viruses are ubiquitous in the population (except HSV-2, HHV-8)
- Primary infections usually inapparent in childhood



ARCHITECTURE



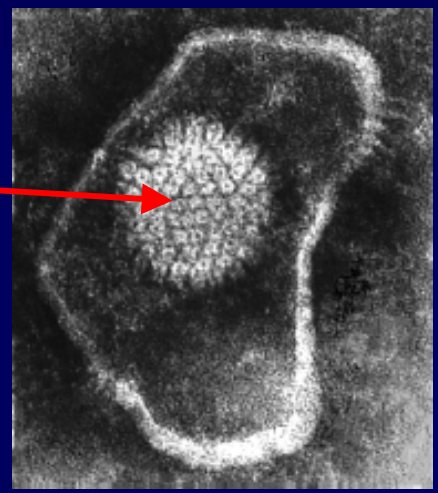
Virion: **Size varies from 130-300 nm**
Variation due to thickness of tegument

***Tegument*:** **Protein structure between capsid and envelope**

***Envelope*:** **Trilaminar membrane derived from cellular membrane.**
Contains glycoprotein spikes (virus coded) on its surface

***Capsid*:** **100-110 nm in diameter has 162 capsomeres**

Core: **Contains linear ds DNA**



Herpes Viral Genome

Herpesviruses have large genomes (up to 235kbp DNA), and are complex viruses containing ~35 virion proteins.

Herpesviruses are widely separated in terms of genomic sequence and proteins, but all are similar in terms of virion structure and genome organization.

All herpesvirus genomes have a unique long (UL) and a unique short (US) region, bounded by inverted repeats (allow rearrangements of the unique regions)

Herpesvirus genomes also contain multiple repeated sequences

- genome size of various isolates of a particular virus can vary by up to 10kbp.

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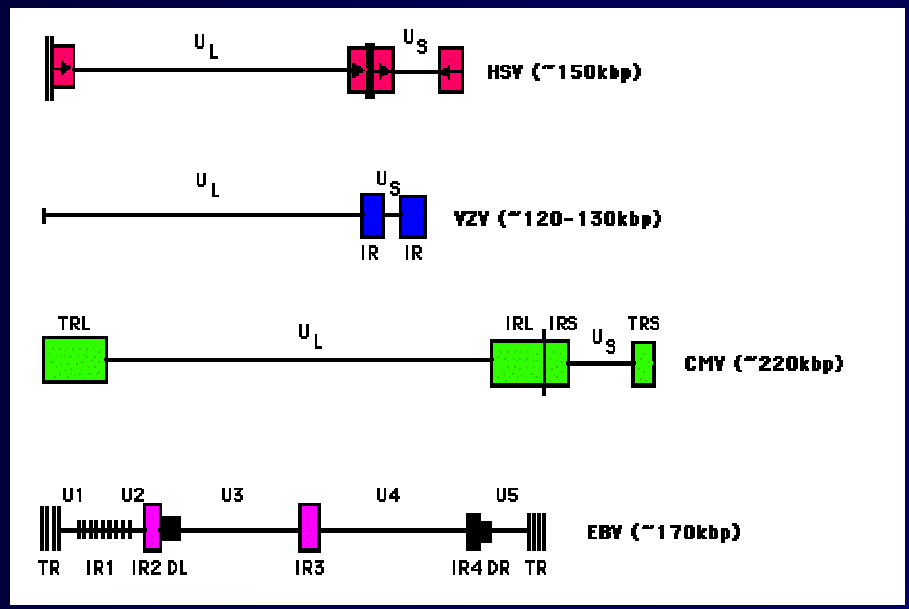
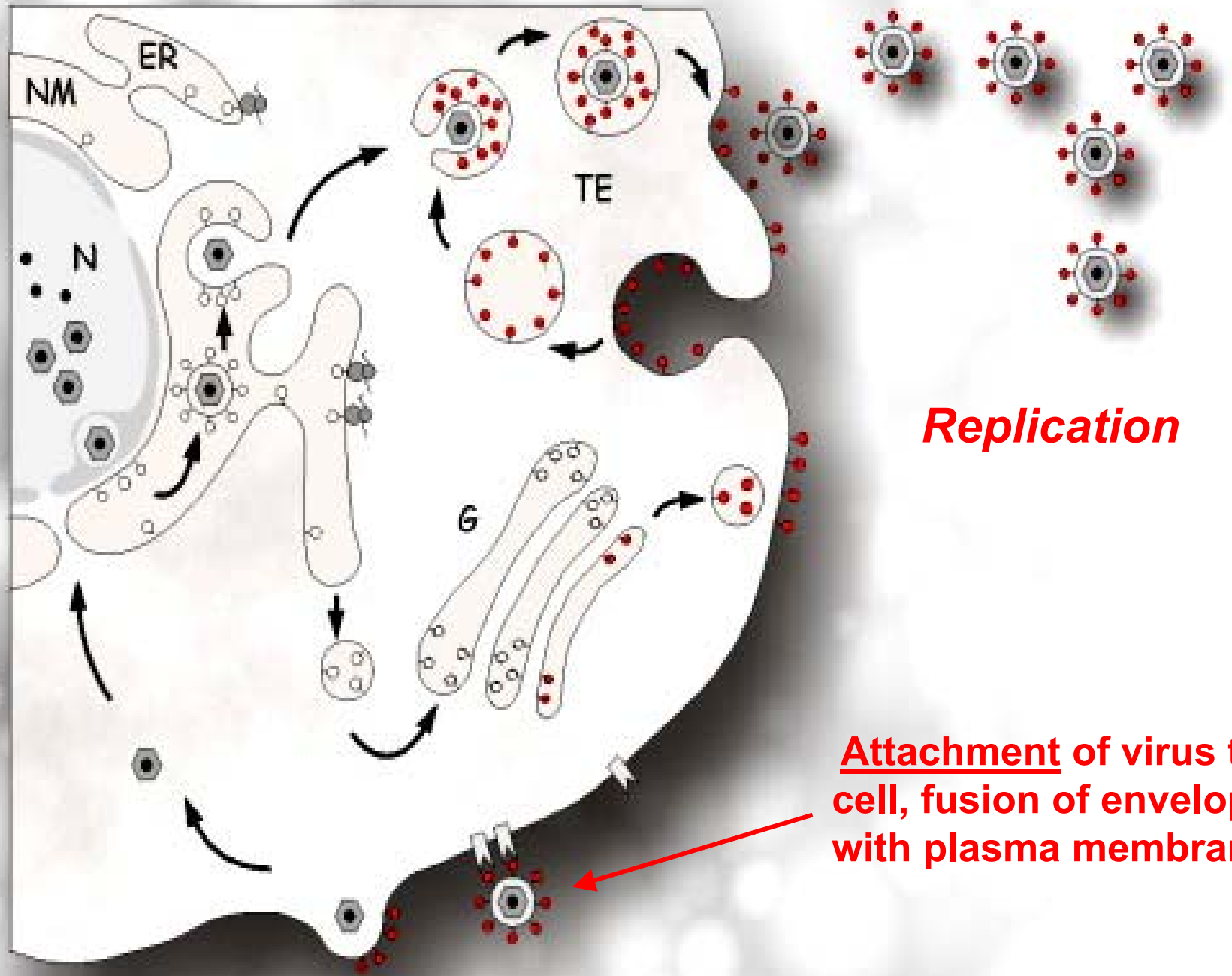


Replication of Herpesviruses



Replication

<u>Attachment</u> of virus to cell, fusion of envelope with plasma membrane

STAGES OF INFECTION

Attachment

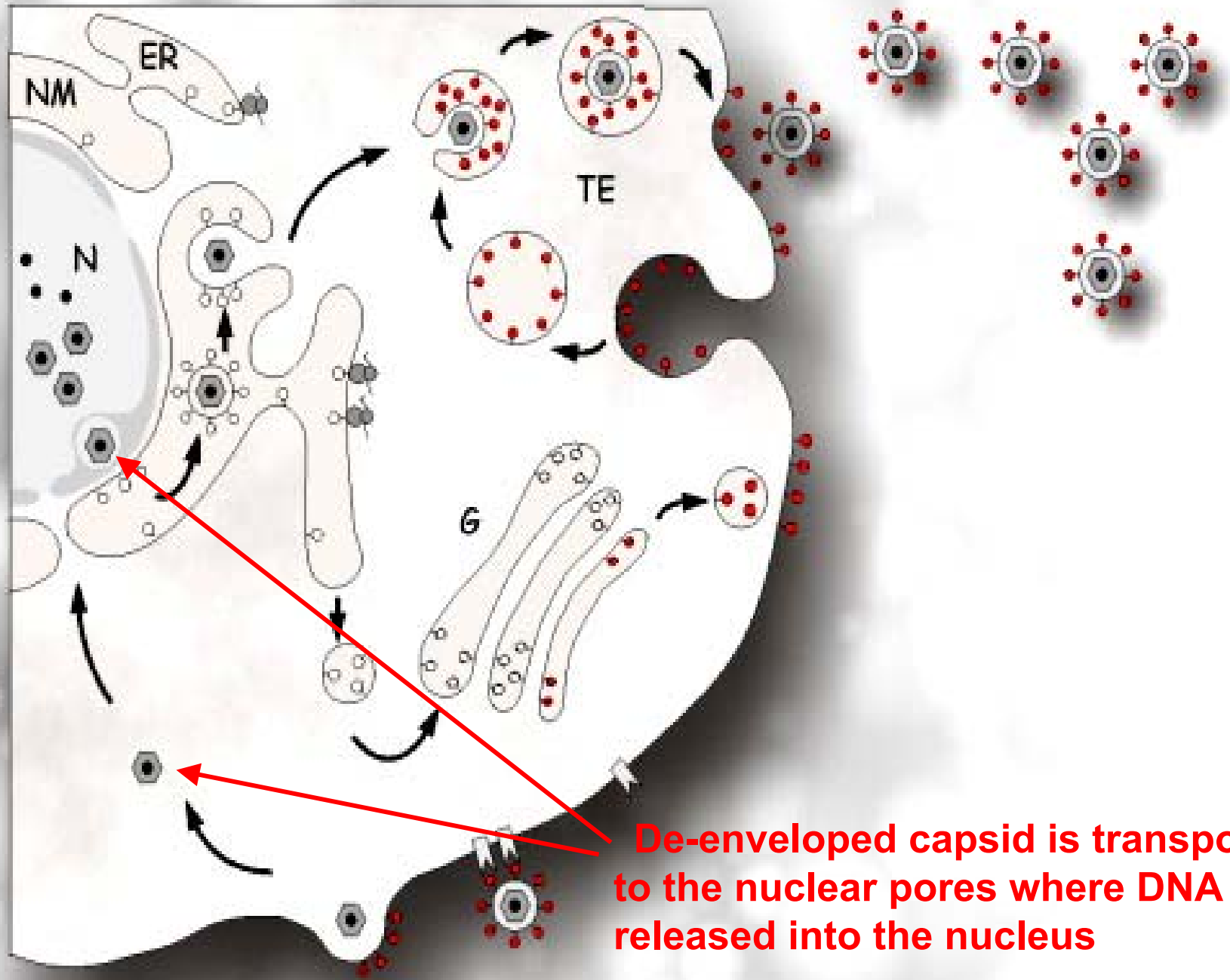
For HSV cell surface heparin sulphate is major binding factor.
Removal of HS does not remove attachment completely.

Most herpesviruses use more than one attachment pathway

Penetration

Mediated by viral surface proteins – fusion of viral envelope with cell plasma membrane.

gB, gD and gH are all involved in fusion



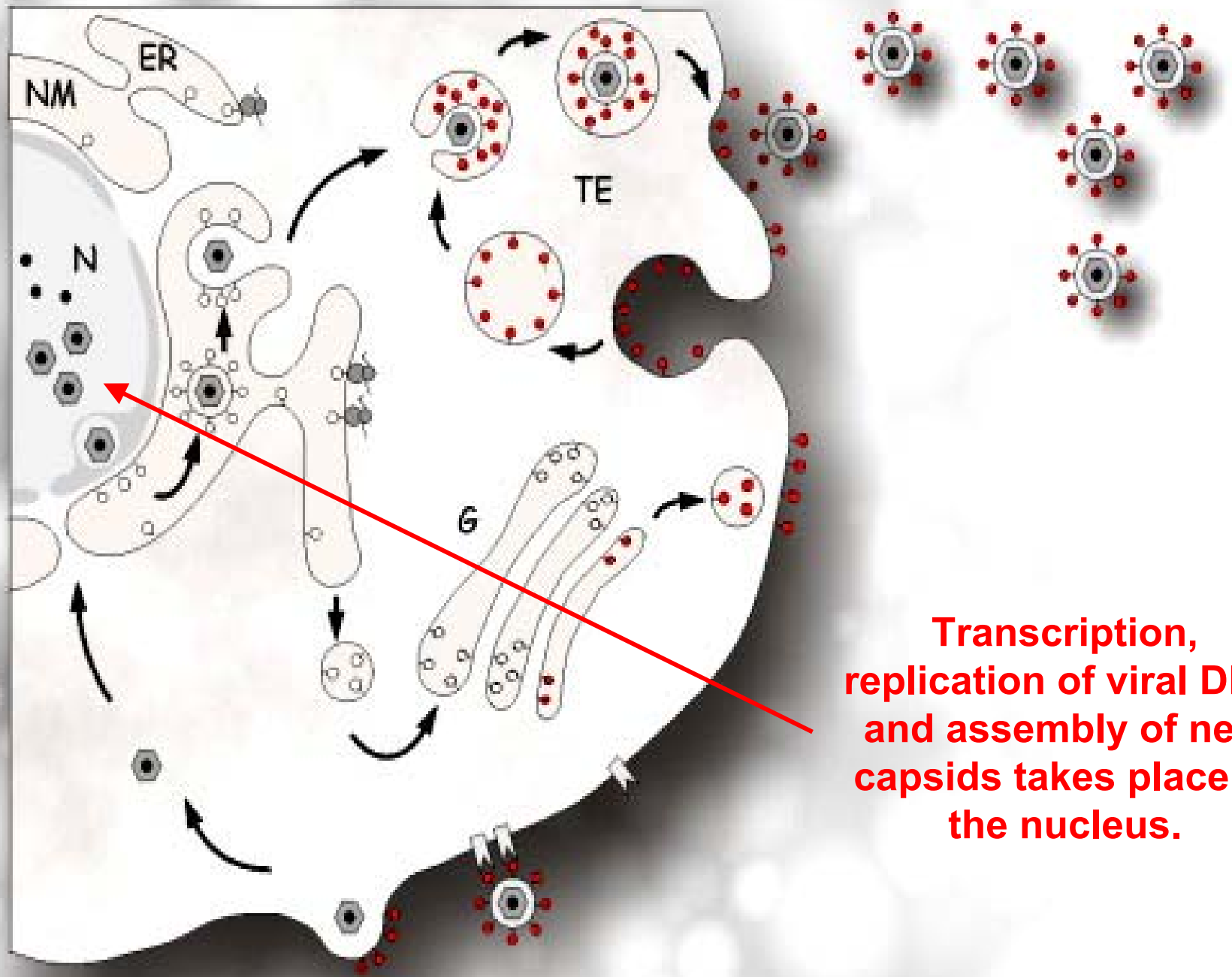
De-enveloped capsid is transported to the nuclear pores where DNA is released into the nucleus

STAGES OF INFECTION

Transport

Release of viral DNA into the nucleus is mediated by an unidentified viral function

Cellular cytoskeleton mediates capsid transport to the nuclear pores.



Transcription, replication of viral DNA and assembly of new capsids takes place in the nucleus.

STAGES OF INFECTION

Replication

Virion components are involved in shutdown of host cell protein synthesis

Virus proteins also induce gene expression (tegument protein --> ∝ genes)

39 of the 73 open reading frames are dispensable. These proteins may be substituted by cellular proteins during productive infection

STAGES OF INFECTION

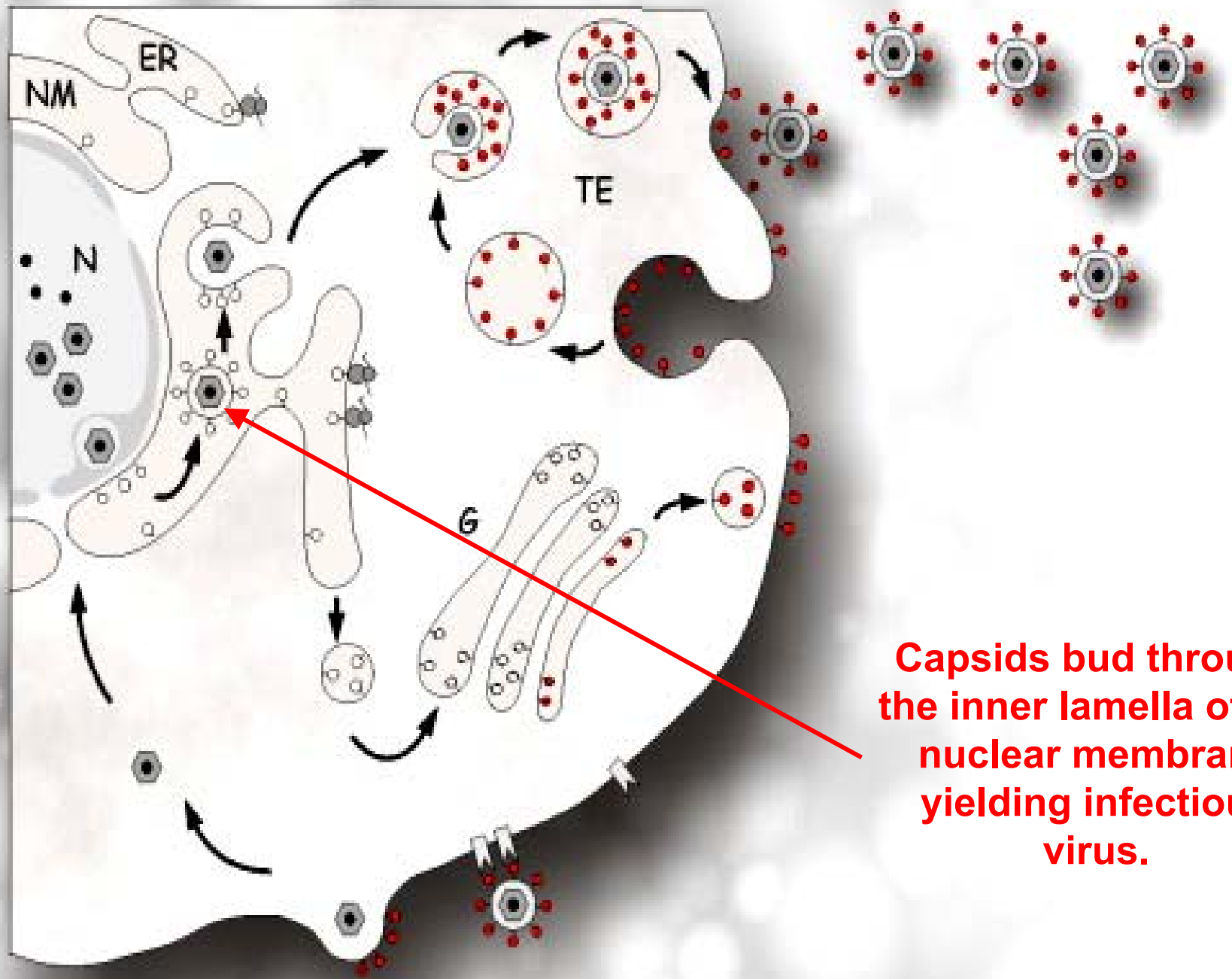
Gene Expression

Gene expression follows a sequential process. First ∝ genes are expressed, followed by β and γ genes.

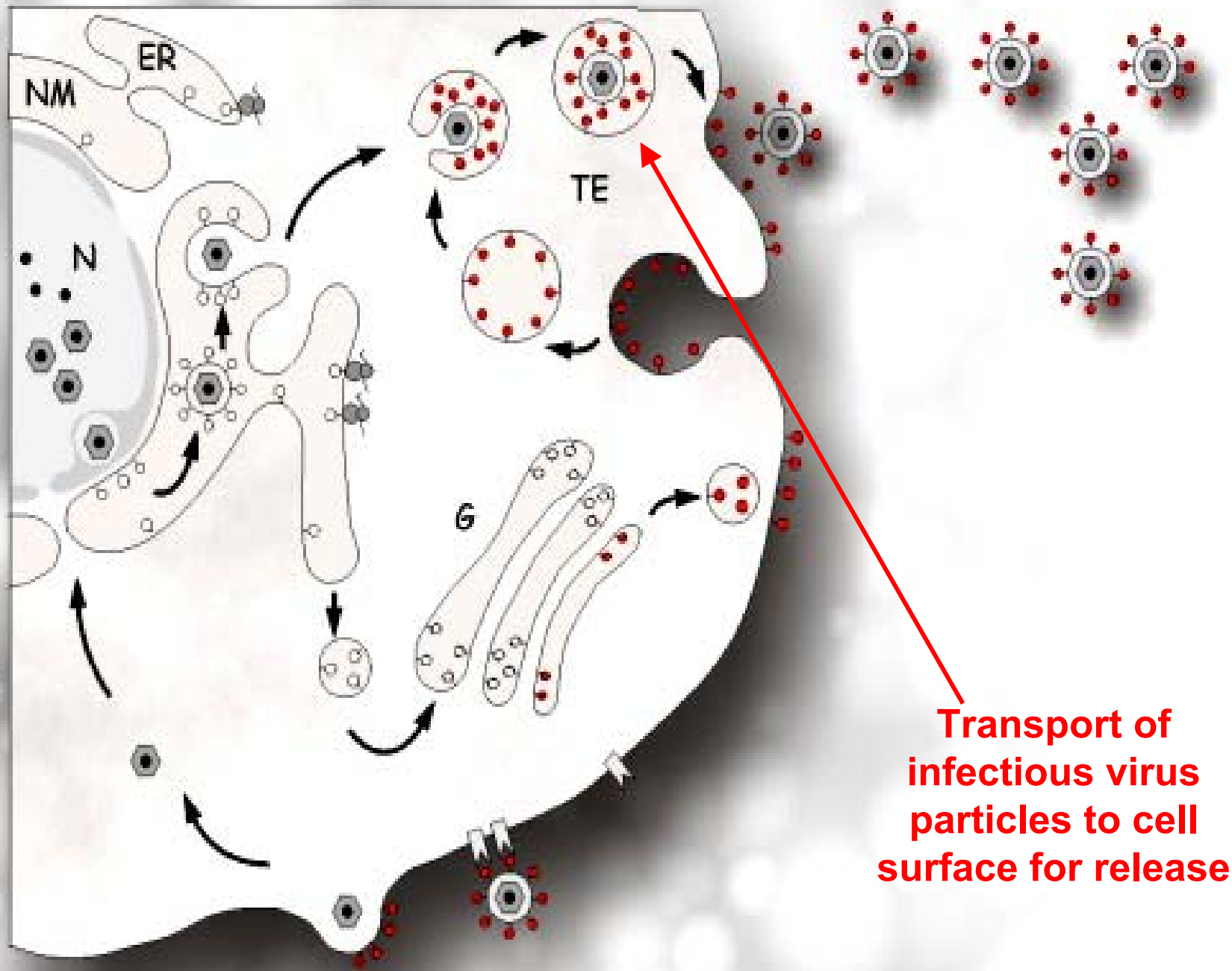
∝ genes are expressed (5 ∝ proteins) in the absence of viral protein synthesis

β genes are only expressed in the presence of competent ∝ proteins. Signals onset of viral DNA synthesis. Involved in viral nucleic acid metabolism

γ genes depend on viral DNA synthesis for expression. Includes genes coding for viral glycoproteins.



Capsids bud through the inner lamella of the nuclear membrane yielding infectious virus.


ER
NM
N
TE
G
Transport of infectious virus particles to cell surface for release

Fate of the Host Cell

With some HV, cells are productively infected (HSV) and do not survive, due to major structural and biochemical alterations.

Others are non-lytic (EBV) and integrate into host-cell genome

Common changes in host cell:

1. Distortion or changes in cell nucleus
2. Changes in appearance of cellular membranes
3. Viral proteins (gD) appear in cell membrane

NOMENCLATURE AND CLASSIFICATION

The family HERPESVIRIDAE has been classified into three subfamilies on the basis of their biological properties and DNA sequence homology and genome arrangement.

Alpha-herpesvirinae

Beta-herpesvirinae

Gamma-herpesvirinae

To date, there are 8 known human Herpesviruses.

Alphaherpesvirinae:

- variable host range, short reproductive cycle, rapid spread in cell culture

Simplexvirus	human herpesvirus 1, 2 (HSV-1, HSV-2)
Varicellovirus	human herpesvirus 3 (VZV)

Betaherpesvirinae:

- restricted host range, long reproductive cycle, enlargement of infected cells

Cytomegalovirus	human herpesvirus 5 (HCMV)
Roseolovirus	human herpesvirus 6, 7 (HHV-6, HHV-7)

Gammaherpesvirinae:

-replicate in lymphoblastoid cells, specific for T or B cells

Lymphocryptovirus	human herpesvirus 4 (EBV)
Rhadinovirus	human herpesvirus 8 (HHV-8)

BIOLOGICAL PROPERTIES

Herpesviruses share 4 significant biological properties

1. All herpesviruses code for a large array of enzymes involved in nucleic acid metabolism and protein processing

2. DNA synthesis and viral assembly occurs in the cell nucleus. Envelopment of capsids occurs on transit through the nuclear membrane.

3. Production of progeny virus results in host cell destruction

4. Herpesviruses can remain latent in the host. In cells harboring latent virus, the viral genome is a circular molecule, and only a small subset of viral genes is expressed (LAT).

BIOLOGICAL PROPERTIES

However, herpesviruses may also vary greatly in biological properties.

- **Some have a wide cell host range (HSV), others have a narrow host range (EBV, HHV-6)**
- **Some multiply rapidly (HSV), others are slow (CMV, VZV)**
- **Individual HV remain latent in a specific set of cells. Cell type differs from one genus to the other. (eg HSV = sensory neurones; EBV = B lymphocytes)**
- **Herpesviruses differ with respect to the clinical manifestations of disease they cause**

Herpes viruses

- Herpesviruses cause chronic / latent / recurrent infections.
- Epidemiology of the common Herpesvirus infections puzzled clinicians for many years.

  In 1950, Burnet and Buddingh showed that HSV could become latent after a primary infection, becoming reactivated after later provocation.

  Weller (1954) isolated VZV (HHV-3) from chicken pox and zoster, indicating the same causal agent.

LATENCY

The ability of HV to remain latent in the human host is unique

For HSV

- Virus enters the body via primary site (epithelial cells)
- Transport to sensory nerves to produce latent state
- During latency virus genome forms circular DNA
- Limited expression of some viral genes occurs (LAT)
- In a fraction of neurones the virus is periodically reactivated
- Virus is carried back to peripheral tissues by axonal transport usually to the site of initial infection
- Severity of lesions is depended on the hosts immune response

Selected genes involved in immune evasion

Function	Gene (Protein)/Virus
Direct infection of immune cells	HCMV *(dendritic/myeloid precursor cells)*; HHV-6 *(NK, T cells)*; HHV-7 *(CD4+ T cells)*
Inhibition of T cell antigen recognition:	
(1) Inhibition of cell-surface class I MHC expression	(1) HCMV US2, US11, US3
(2) TAP inhibition (transporter associated with antigen presentation)	(2) HSV-1 ICP47; HCMV US6
(3) blockers of antigen processing/presentation	(3) EBV EBNA-1; HCMV pp65
Inhibition of natural killer cell attack	HCMV US18 *(MHC class I homolog; engages an inhibitory receptor on NK cells with high affinity)*
Inhibition of apoptosis *(may interfere with cytotoxic T cell attack)*	HHV-8 ORF 71 *(a viral FLICE-inhibitory protein or v-FLIP)*; v-*bcl-2* (EBV, HHV-8)
Sequestration of chemokines	HCMV US28 *(chemokine receptor homolog)*; HHV-8 ORF 74 *(ditto)*
Cytokine and chemokine homologs	EBV BCRF1 (*IL-10 homolog*, *IL-10 favors T_H2 T cell responses*); HHV-8 vMIP-II *(chemokine antagonist)*;
Complement- and interferon - interacting molecules	HSV-1 gC *(binds and inactivates C3)*; EBV EBERs *(block interferon)*

http://darwin.bio.uci.edu/~faculty/wagner/movieindex.html

http://www.tulane.edu/~dmsander/garryfavweb.html