ADENOVIRUS

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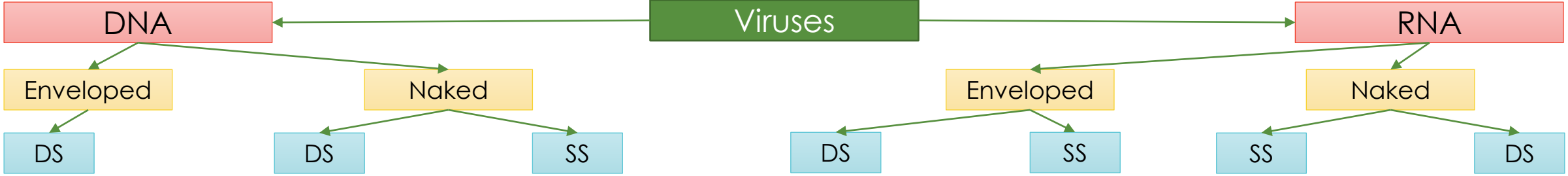


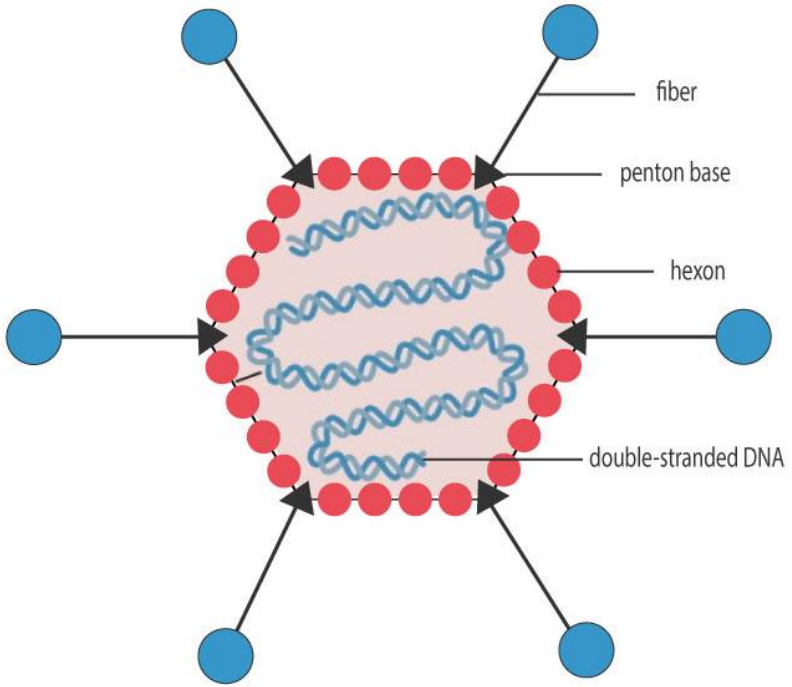
Adenoviridae (Ic) Adenovirus

Parvoviridae (Ic) Parvovirus B19, Bocaviruses

Guidelines:
SS: single stranded
DS: Double stranded
Ic: Ichosahedral capsid
He: Helical capsid
Co: Complex capsid

Adenovirus

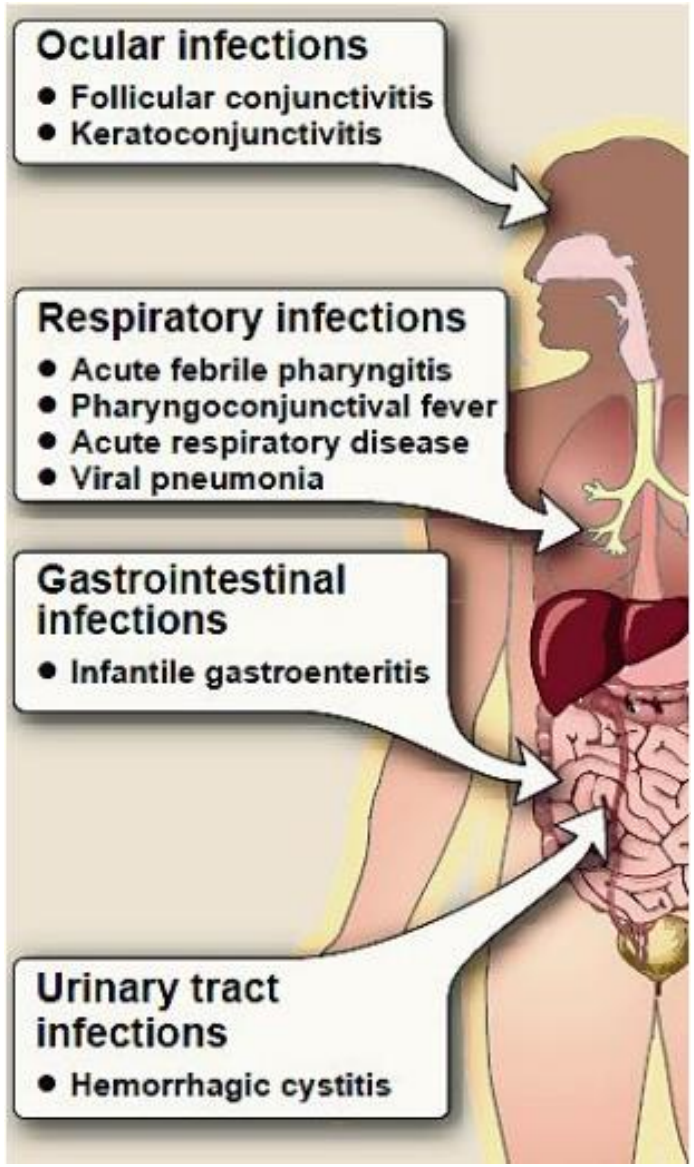
1. Structure of the virus



2. Replication

- Just have a general idea
1. Virus enter the cell by endocytosis through coxsackie–adenovirus receptor
2. Replication occurs in the nucleus when the cell is in the s phase
3. Capsid forms before the genetic material enter the virus
4. infectious cycle takes about 24 hours
5. Adenoviruses are not thought to be important in human cancer causation

3- Pathogenesis & clinical findings



4- Laboratory Diagnosis

- Viral culture
- Hybridization
- PCR: can detect also the serotype that is determined by the hexon gene
- shell viral technique
- detect in stool by some techniques
- antibody-titer detecting

5- Epidemiology

= Perennial (not seasonal) mostly sporadic
= common serotypes: 1, 2, 3, 5, 7, 40 & 41
= Transmission via direct contact, fecal–oral route, by respiratory droplets, or contaminated fomites
= Many infections are subclinical

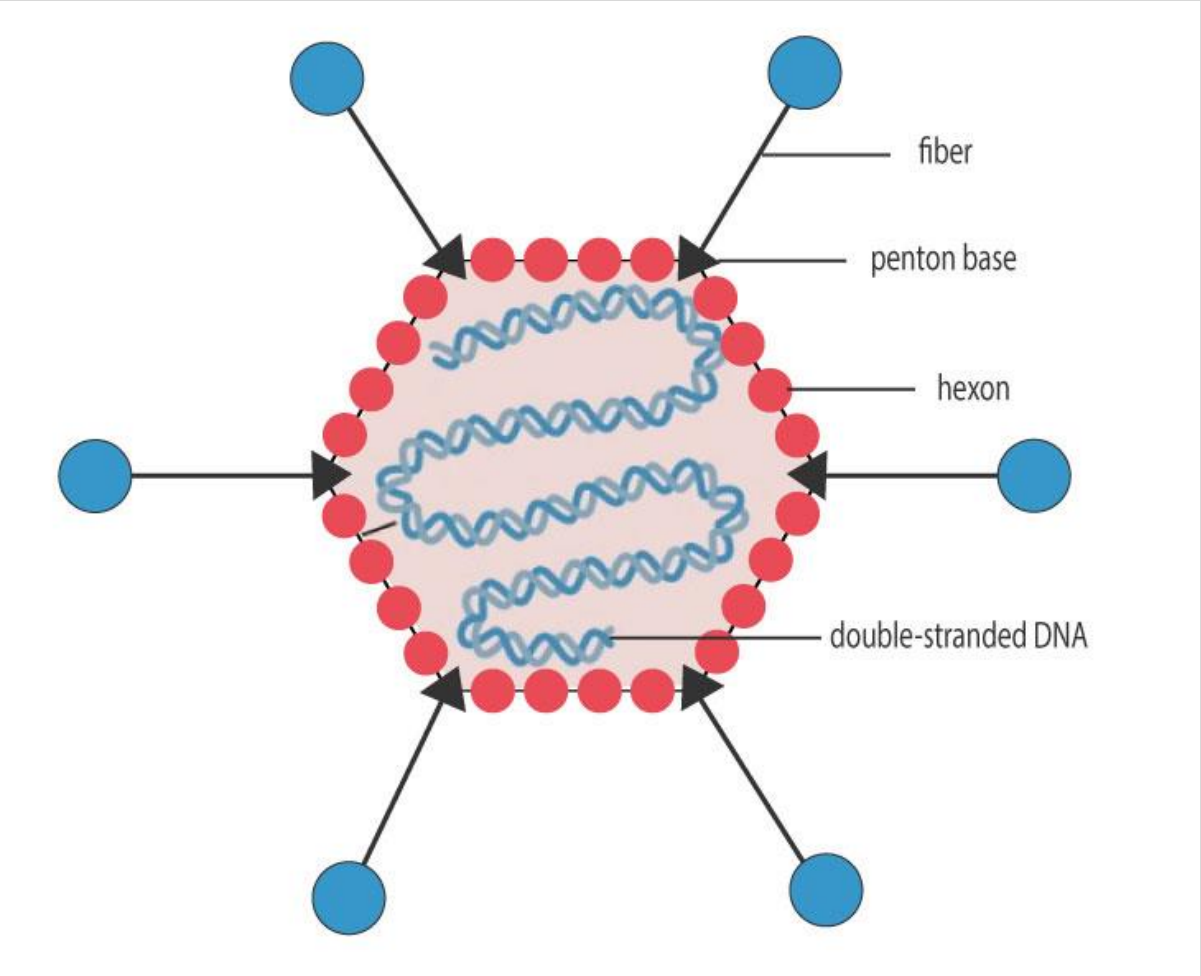
6- Treatment, Prevention and Control

- Sanitation
- No anti-viral drugs
- Oral vaccines for types 4 and 7

1- Structure of the virus

Important for replication

Virion: Icosahedral, 70–90 nm in diameter, 252 capsomeres; fiber projects from each vertex
Composition: DNA (13%), protein (87%)
Genome: Double-stranded DNA, linear, 26–45 kbp, protein bound to termini, infectious
Proteins: Important antigens (hexon, penton base, fiber) are associated with the major outer capsid proteins
Envelope: None
Replication: Nucleus
Outstanding characteristic: Excellent models for molecular studies of eukaryotic cell processes



1- Structure of the virus

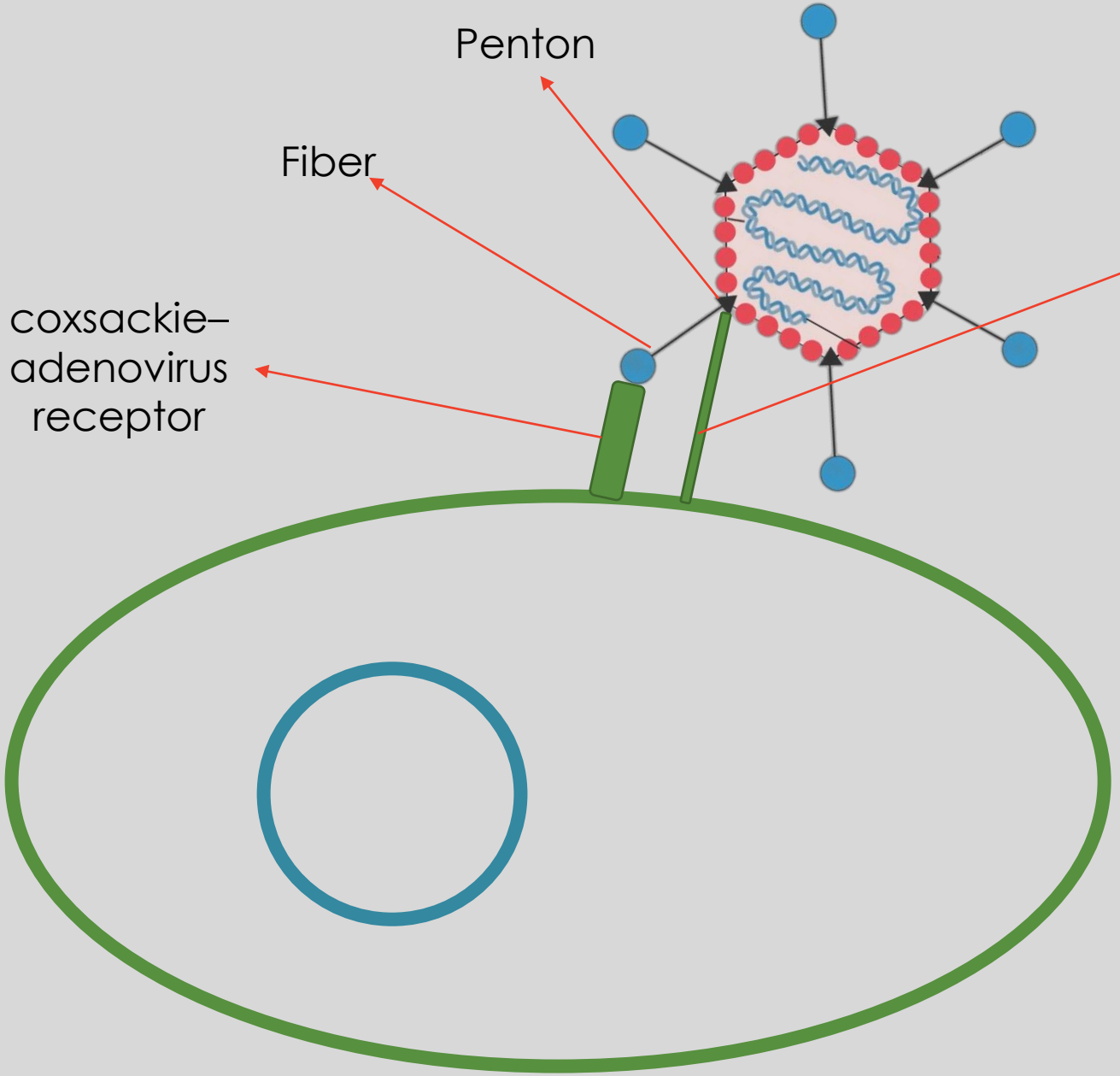
There are 57 serotypes

There are 7 groups

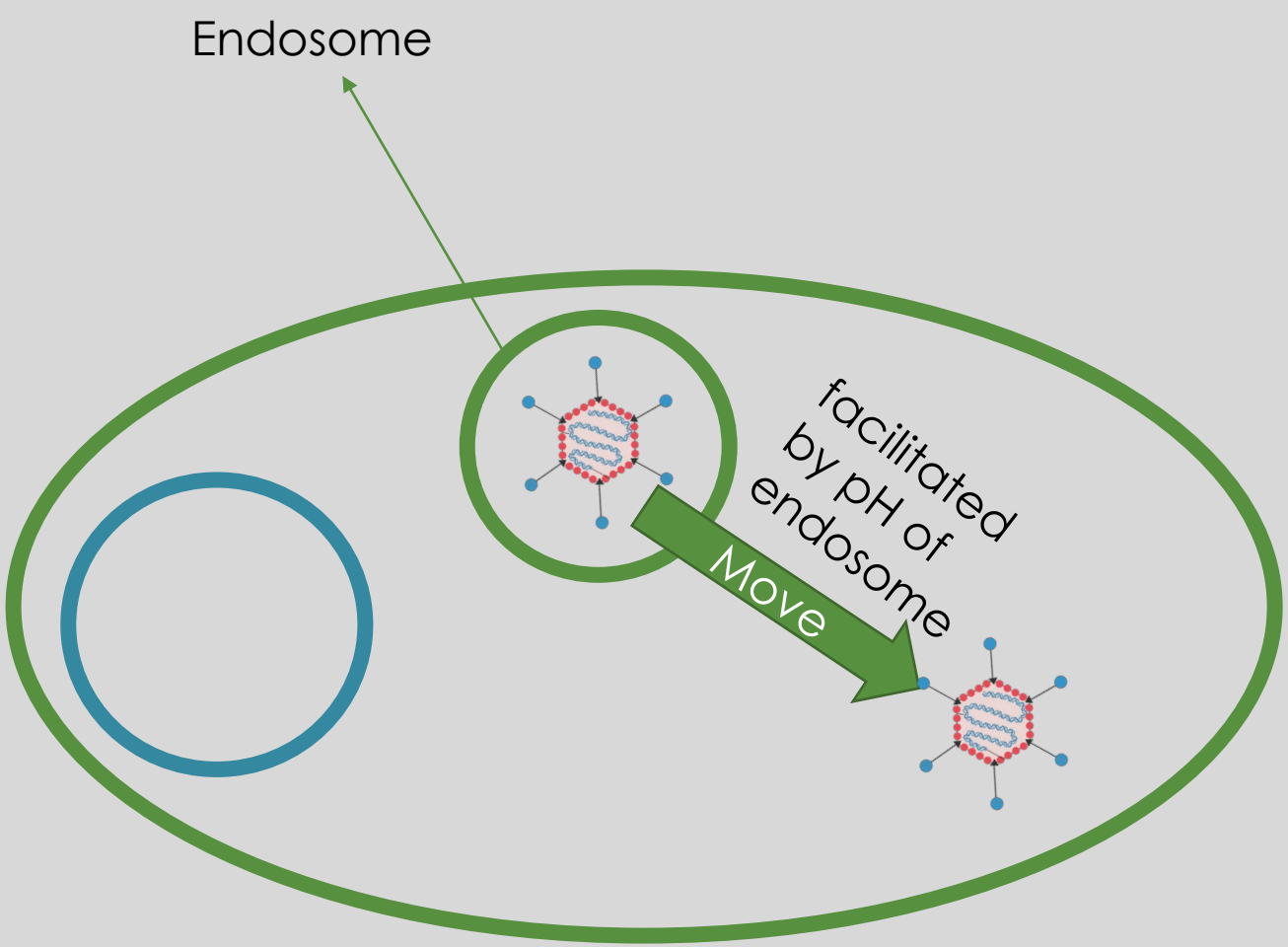
Group	Serotypes	Hemagglutination		Percentage of G + C[a] in DNA	Oncogenic Potential	
		Group	Result		Tumorigenicity in Vivo[b]	Transformation of Cells
A	12, 18, 31	IV	None	48–49	High	+
B	3, 7, 11, 14, 16, 21, 34, 35, 50	I	Monkey (complete)	50–52	Moderate	+
C	1, 2, 5, 6	III	Rat (partial)	57–59	Low or none	+
D	8–10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49, 51	II	Rat (complete)	57–61	Low or none[c]	+
E	4	III	Rat (partial)	57	Low or none	+
F	40, 41	III	Rat (partial)	57–59	Low or none	+

Most common to cause infections

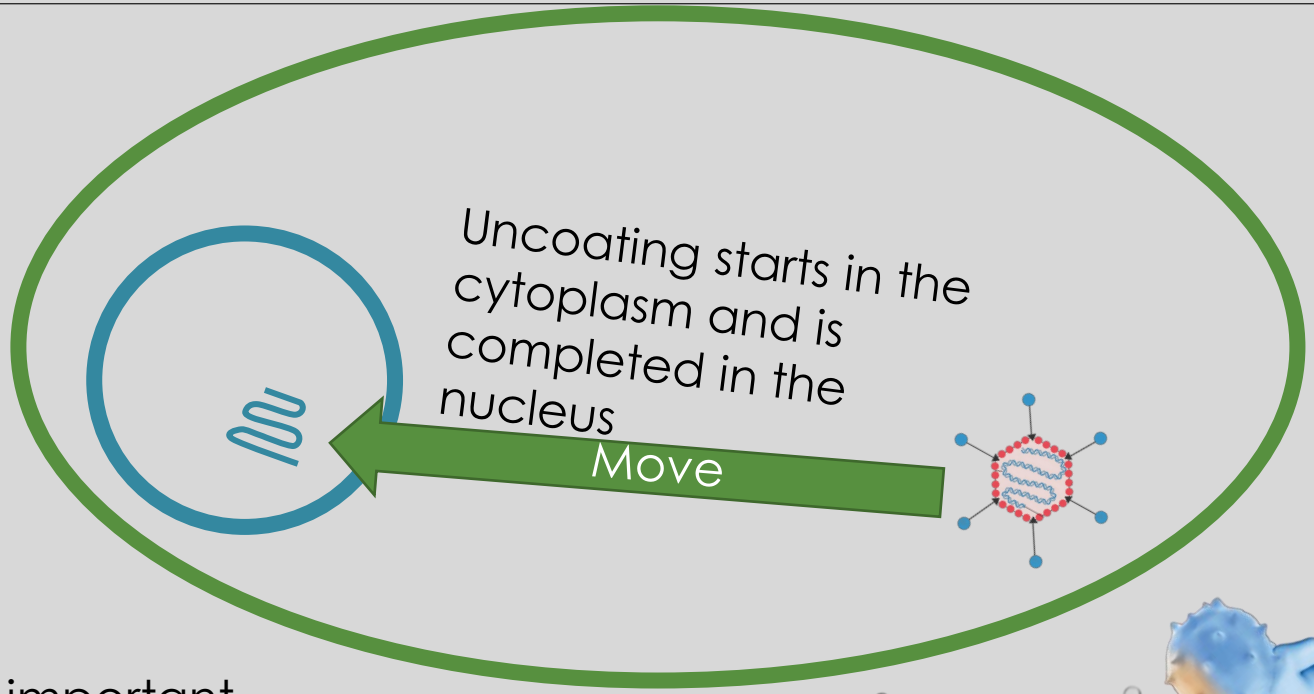
Cause gastroenteritis infections



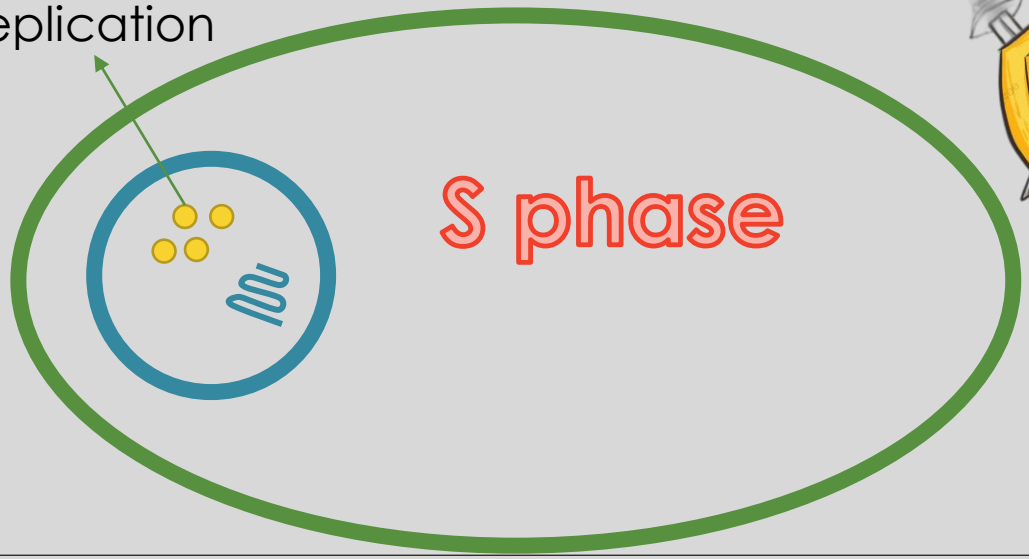
1) Fiber attaches cellular receptors (e.g. coxsackie–adenovirus receptor, a member of the Immuno-globulin super family); the interaction of the penton base with cellular integrins promotes the internalization step

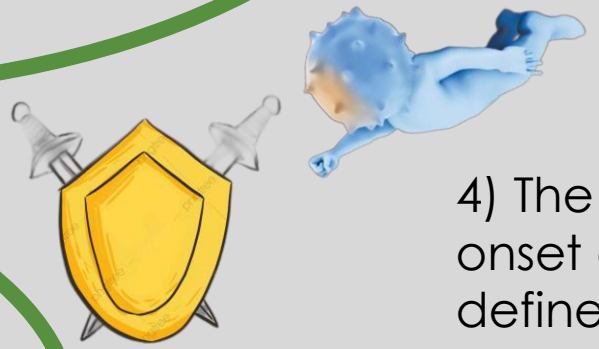


2) Adsorbed virus is internalized into endosomes; the majority of particles (~90%) move rapidly from endosomes into the cytosol (half-life ~5 minutes) facilitated by the acidic pH of the endosome



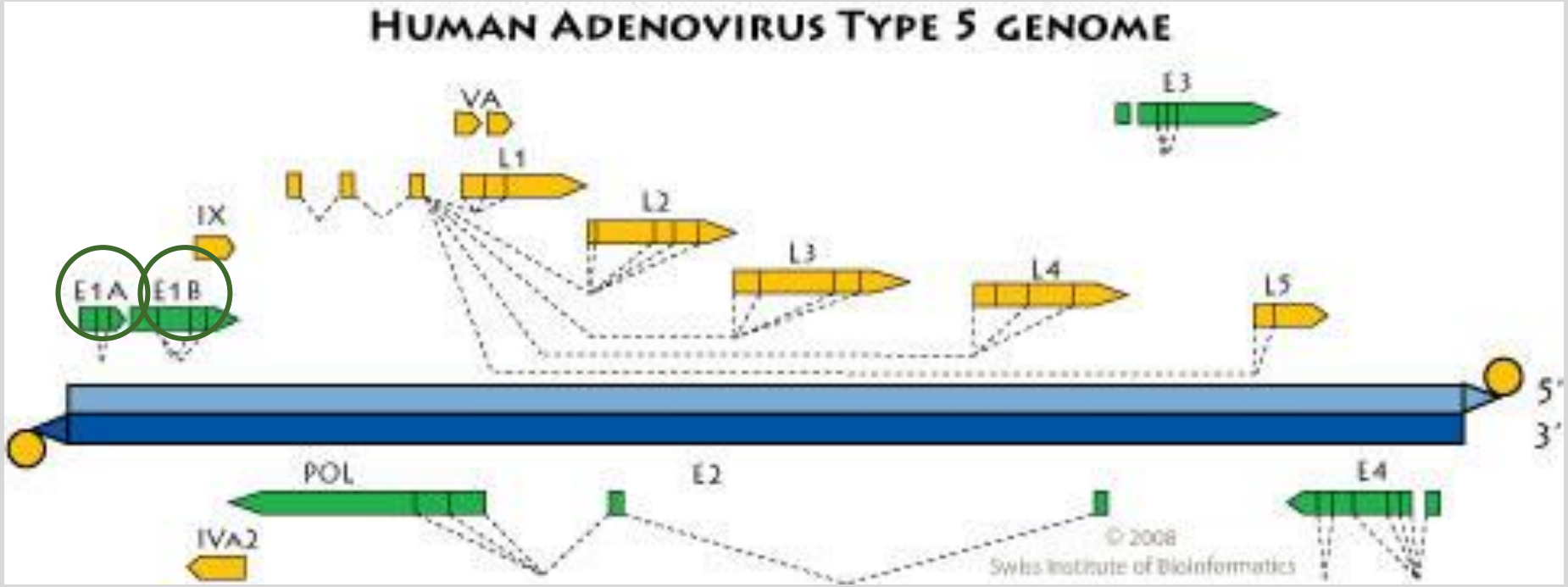
3) Uncoating starts in the cytoplasm and is completed in the nucleus, with release of the DNA where the replication will start





4) The steps that occur before the onset of viral DNA synthesis are defined as early events; initiated to induce the host cell to enter the S phase, to express viral evade mechanisms, and to synthesize viral gene products needed for viral DNA replication (called early proteins)

5) The E transcripts come from seven separated regions of the viral genome with synthesis of more than 20 early proteins, many of which are NS



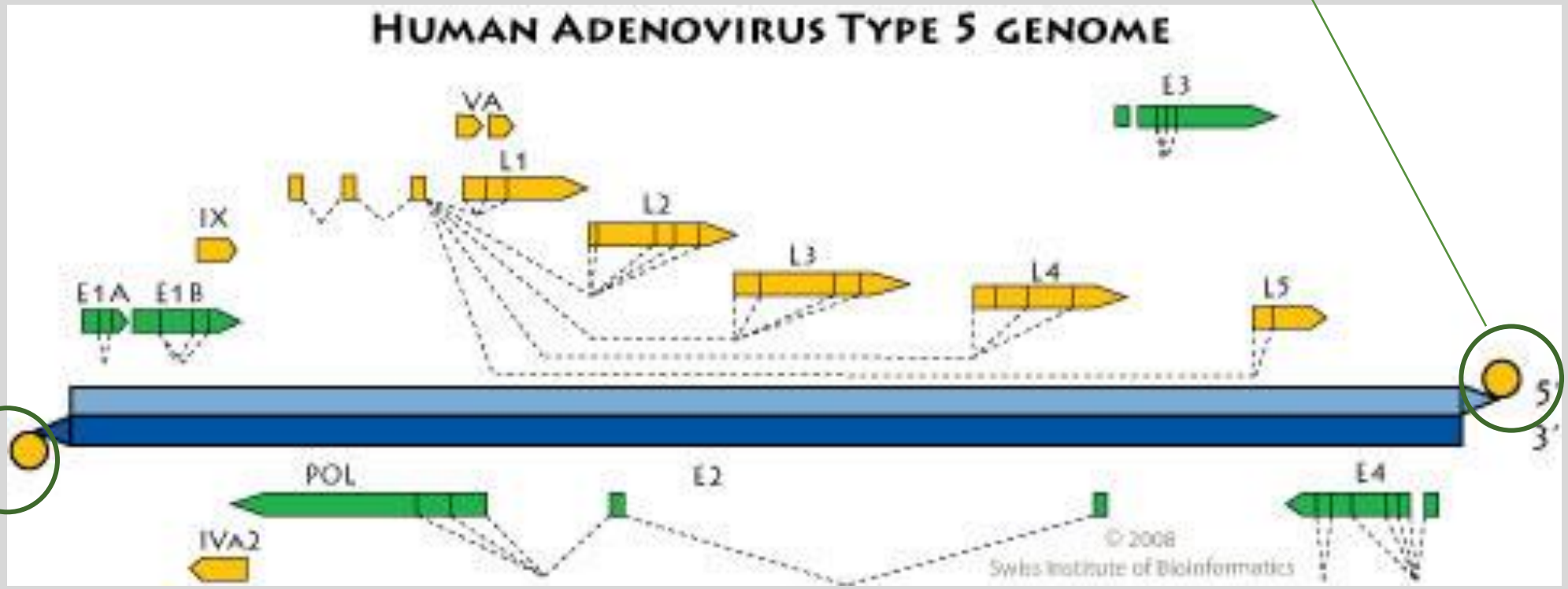
6) The E1A early gene is important; it must be expressed for the other early regions to be transcribed

7) The E1B early region encodes proteins that block cell death (apoptosis); this is necessary to prevent premature cell death that would adversely affect virus yields

8) The E1A and E1B regions contain the only adenovirus genes involved in cell transformation; those gene products bind cellular proteins (e.g., pRb, p300, p53) that regulate cell cycle progression

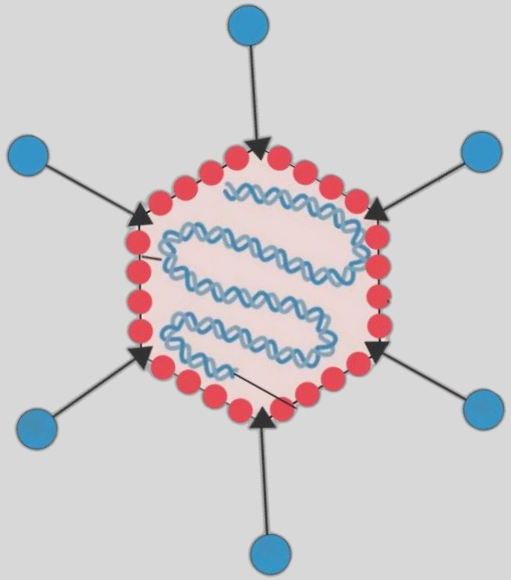
9) Adenovirus E3 region proteins, which are nonessential for viral growth in tissue culture, inhibit cytolysis of infected cells by host responses. The E3 gp19-kDa protein blocks movement of MHC-I to the cell surface

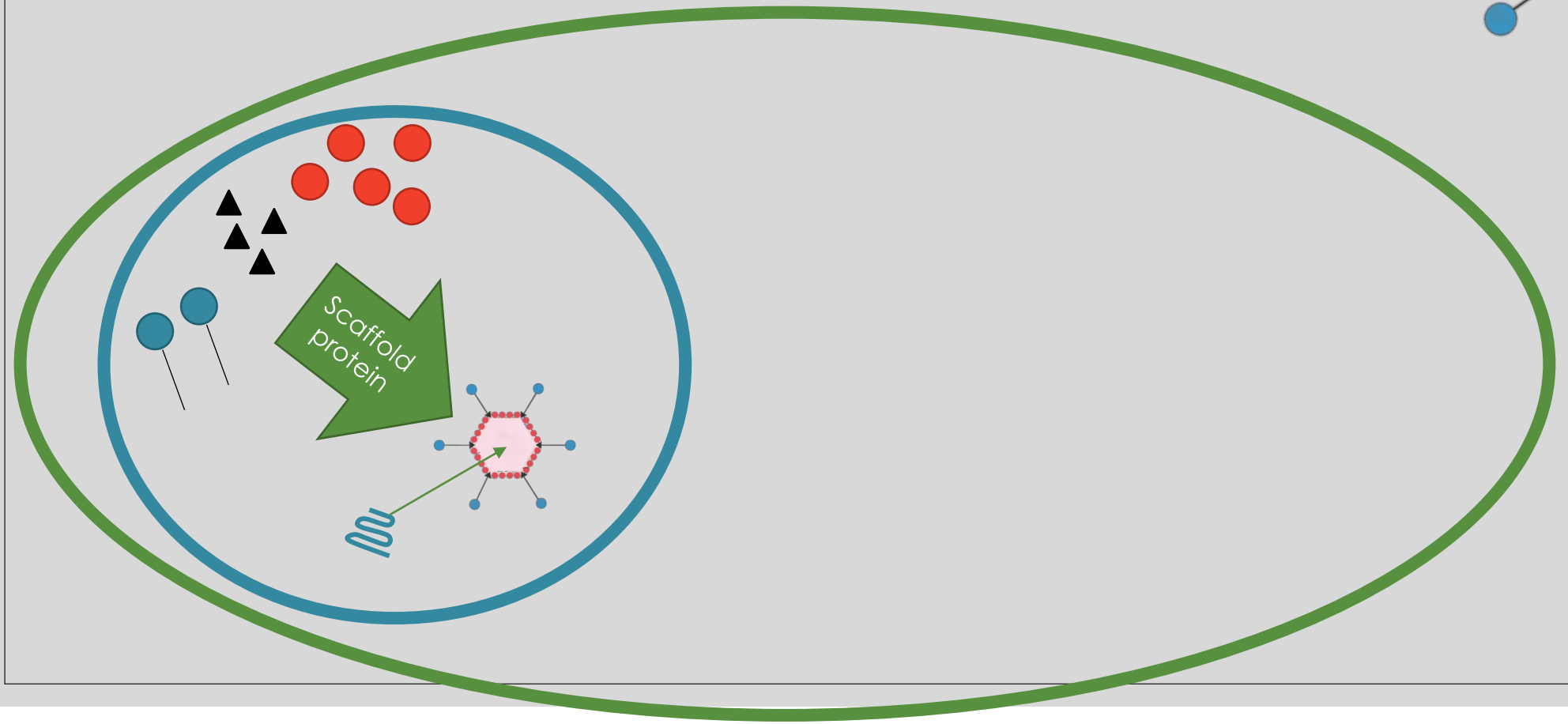
10) The virus-encoded, covalently linked terminal protein functions as a primer for initiation of viral DNA synthesis



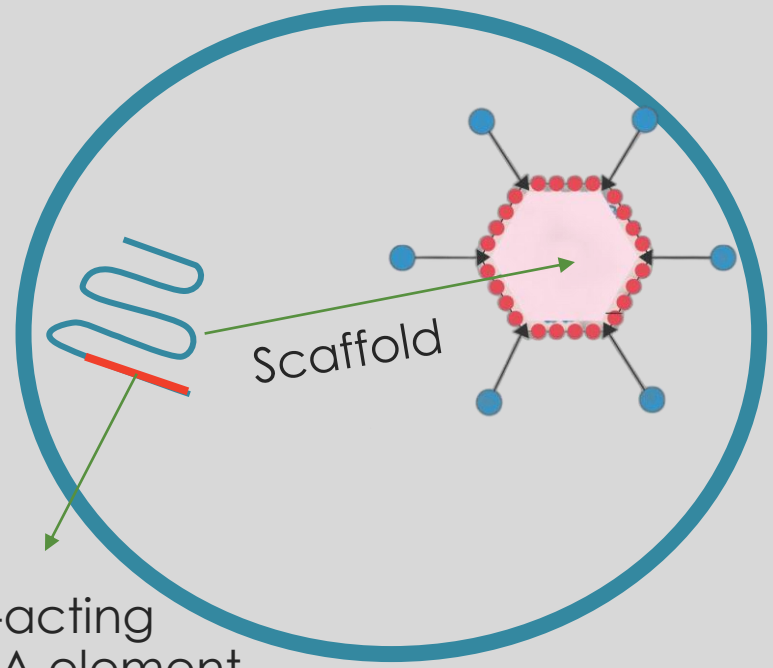
11) Late events begin concomitantly with the onset of viral DNA synthesis. The major late promoter controls the expression of the late ("L") genes coding for viral structural proteins.
12) There is a single large primary transcript (~29,000 nucleotides in length) that is processed by splicing to generate at least 18 different late mRNAs.
13) A complex involving the E1B 55-kDa polypeptide and the E4 34-kDa polypeptide inhibits the cytoplasmic accumulation of cellular mRNAs

14) Virion morphogenesis occurs in the nucleus. Each hexon capsomere is a trimer of identical polypeptides. The penton is composed of five penton base polypeptides and three fiber polypeptides
15) A late L4-encoded "scaffold protein" assists in the aggregation of hexon polypeptides but is not part of the final structure
15) Capsomeres self-assemble into empty-shell capsids in the nucleus. Naked DNA then enters the preformed capsid



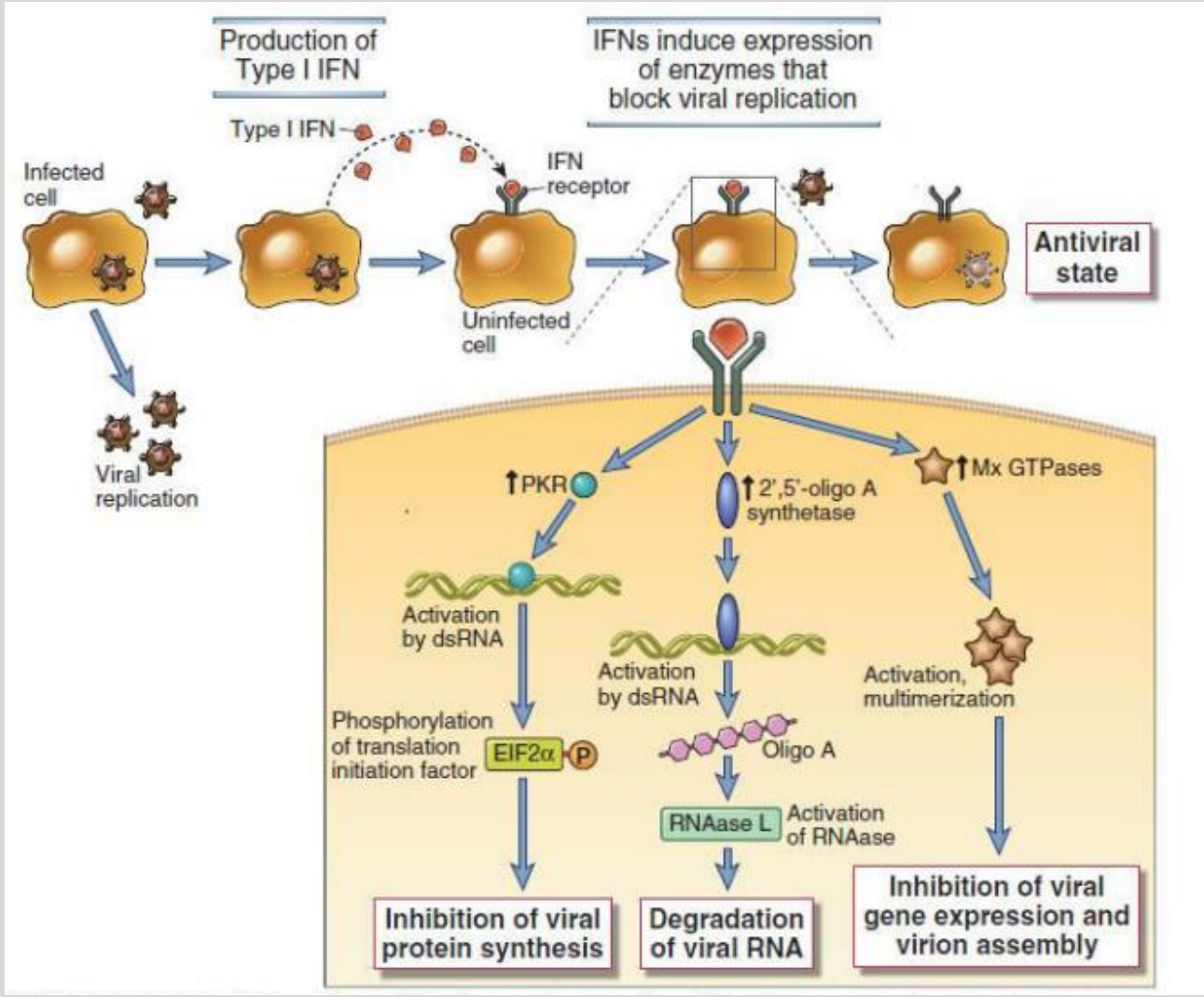


17) A cis-acting DNA element near the left-hand end of the viral chromosome serves as a packaging signal, necessary for the DNA–capsid recognition event. Another viral scaffolding protein, encoded in the L1 group, facilitates DNA encapsidation.



18) Finally, precursor core proteins are cleaved "virus-encoded cysteine proteinase", which allows the particle to tighten its configuration, and the pentons are added

The small, abundant viral RNAs afford protection from the antiviral effect of interferon by preventing activation of an interferon-inducible kinase that phosphorylates and inactivates eukaryotic initiation factor 2



2- Replication

- So: to sum up about proteins:
  1- E1A :must be expressed for the other early regions to be transcribed
  2- E1B : encodes proteins that block cell death (apoptosis)
  3- e E1A and E1B regions contain the only adenovirus genes involved in cell transformation by regulating cell cycle progression
  4- e E1B 55-kDa polypeptide and the E4 34-kDa polypeptide forms a complex that inhibits the cytoplasmic accumulation of cellular mRNAs
  5- The E3 gp19-kDa protein blocks movement of MHC-I to the cell surface
  6- L4-encoded "scaffold protein" assists in the aggregation of hexon polypeptides but is not part of the final structure
  7- a scaffolding protein, encoded in the L1 group, facilitates DNA encapsidation.

2- Replication

- The mature particle is then stable, infectious, and resistant to nucleases
- The adenovirus infectious cycle takes about 24 hours
- The cytopathic effect usually consists of marked rounding, enlargement, and aggregation of affected cells into grapelike clusters.
- Adenoviruses are not thought to be important in human cancer causation

3- Pathogenesis & clinical findings

- Adenoviruses infect and replicate in epithelial cells of the respiratory tract, eye, gastrointestinal tract, and urinary tract, causing their lysis and inducing inflammation, this will cause a variety of symptoms
- They usually do not spread beyond the regional lymph nodes.
- Group C viruses persist as latent infections for years in adenoids and tonsils and are shed in the feces for many months after the initial infection. In fact, the name "adenovirus" reflects the recovery of the initial isolate from explants of human adenoids.
- About one-third of the known human serotypes are commonly associated with human illness.
- A single serotype may cause different clinical diseases and, conversely, that more than one type may cause the same clinical illness, some are subclinical.
- Adenoviruses 1–7 are the most common types worldwide
- Most infections are mild and self-limited, exept for immunocompromised people it might be fatal

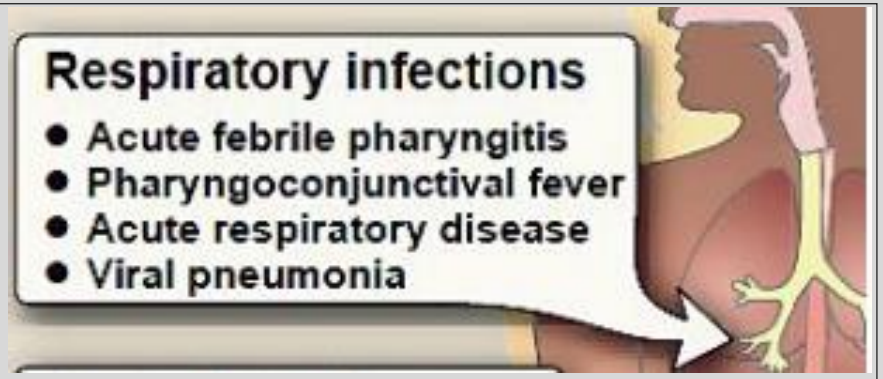
3- Pathogenesis & clinical findings

- For eye infections:
- 1) Follicular conjunctivitis: inflammation of conjunctiva
  → The duration of conjunctivitis is 1–2 weeks, and complete recovery with no lasting sequelae is the common outcome
- 2) Keratoconjunctivitis (more severe): acute conjunctivitis followed by keratitis that usually resolves in 2 weeks but may leave subepithelial opacities in the cornea for up to 2 years.
  → It is caused by types 8, 19, and 37. This disease occurs mainly in adults and is highly contagious. Adenoviruses can remain viable for several weeks on sinks and hand towels, and these may be sources of transmission.

- Additional notes: Symptoms of conjunctivitis are:
  1) Tearing
  2) Redness of the eye
  3) Photophobia
  4) Pain

3- Pathogenesis & clinical findings

- Types of Respiratory infections:
- 1) Acute febrile pharyngitis: Fever + inflammation in pharynx
- 2) Pharyngoconjunctival fever: tends to occur in outbreaks, such as at children's summer camps ("swimming pool conjunctivitis"), and is associated with types 3 and 7
- 3) acute respiratory disease: typical symptoms include cough, nasal congestion, fever, and sore throat. This syndrome is most commonly manifested in infants and children (5% of all infections)
  → Adenoviruses are the cause of an acute respiratory disease syndrome among military recruits (caused by types 4 and 7 and occasionally by type 3)
- 4) pneumonia : Adenoviruses (particularly types 3, 7, and 21) are thought to be responsible for about 10–20% of pneumonias in childhood. Adenoviral pneumonia has been reported to have a mortality rate up to 10% in the very young



- Additional notes:
  Although adenoviruses cause only 2–5% of all respiratory illness in the general population, respiratory disease caused by types 3, 4, and 7 is common among military recruits
  → Symptoms of pharyngitis are: redness in pharynx, cough, sore throat and sometimes nasal congestion
  → Symptoms of pneumonia: hard breathing, chest pain, cough sometimes associated with bleeding

3- Pathogenesis & clinical findings

- Many adenoviruses replicate in intestinal cells and are present in stools, but the presence of most serotypes is not associated with gastrointestinal disease. However, two serotypes (types 40 and 41) have been etiologically associated with infantile gastroenteritis and may account for 5–15% of cases of viral gastroenteritis in young children, the most common symptom is diarrhea
- Most human adenoviruses replicate in intestinal epithelium after ingestion but usually produce subclinical infections rather than overt symptoms.

- Types 11 and 21 may cause acute hemorrhagic cystitis in children. Virus commonly occurs in the urine of such patients, symptoms are painful urination associated with blood

3- Pathogenesis & clinical findings

- Infection is usually self limited, In immunocompromised patients (transplant, AIDS) severe fatal pneumonia, hepatitis, myocardial infection, and severe GI disease
- In contrast to most respiratory infectious agents, the adenoviruses induce effective and long-lasting immunity against reinfection
- Maternal antibodies usually protect infants against severe adenovirus respiratory infections in the first 6 months of the life based on the half-life of the immunoglobulins γ

4- Laboratory Diagnosis

- Duration of adenovirus excretion varies among different illnesses: 1–3 days, throat of adults with common cold; 3–5 days, throat, stool, and eye, for pharyngoconjunctival fever; 2 weeks, eye, for keratoconjunctivitis; 3–6 weeks, throat and stool of children with respiratory illnesses; 2–12 months, urine, throat, and stool of immunocompromised patients.
- Virus culture can be done, Established human epithelial cell lines, such as HEp-2, HeLa, and KB, are sensitive but are difficult to maintain without degeneration for the length of time (28 days) required to detect some slow-growing natural isolates

4- Laboratory Diagnosis

- Infectious adenovirus detection may be made rapidly using the shell vial technique
- PCR assays are routinely used for diagnosis of adenovirus infections in tissue samples or body fluids, usually by using primers from a conserved viral sequence that can detect all serotypes
- PCR assays have been described that use single primer pairs that target conserved segments that bracket a hypervariable region in the hexon gene. The assays can detect all known serotypes of human adenoviruses, and sequencing of the amplicon allows serotype identification

4- Laboratory Diagnosis

- Hybridization or restriction endonuclease digestion patterns can identify an isolate as an adenovirus and group it.
- The fastidious enteric adenoviruses can be detected by direct examination of fecal extracts by electron microscopy, by enzyme-linked immunosorbent assay, or by latex agglutination test.
- Because adenoviruses can persist in the gut and in lymphoid tissue for long periods and because recrudescent viral shedding can be precipitated by other infections, the significance of a viral isolation must be interpreted with caution
- Fourfold or greater rise in complement-fixing antibody titer between acute-phase and convalescent-phase sera indicates recent infection with an adenovirus, but it gives no clue about the specific type involved

5- Epidemiology

- Perennial (not seasonal) mostly sporadic
- The most common serotypes: 1, 2, 3, 5, 7, 40 and 41
- Transmission via direct contact, fecal–oral route, by respiratory droplets, or contaminated fomites
- Many infections are subclinical

6- Treatment, Prevention and Control

- There is no specific treatment for adenovirus infections
- Careful hand washing is the easiest way to prevent infections
- Disinfection of surfaces
- In group settings, paper towel use
- Chlorination of swimming pools and waste water
- Strict asepsis during eye examinations, coupled with adequate sterilization of equipment

6- Treatment, Prevention and Control

- Attempts to control adenovirus infections in the military have focused on vaccines
- Live adenovirus vaccine containing types 4 and 7, encased in gelatin-coated capsules and given orally, was introduced in 1971
- Released in the intestine, where it replicates and induces neutralizing Ab
- It does not spread from a vaccinated person to contacts
- Stopped in 1999 and reintroduced in 2011; high efficacy