Adeno Virus
MIC 2004
MSc Microbiology Semester II

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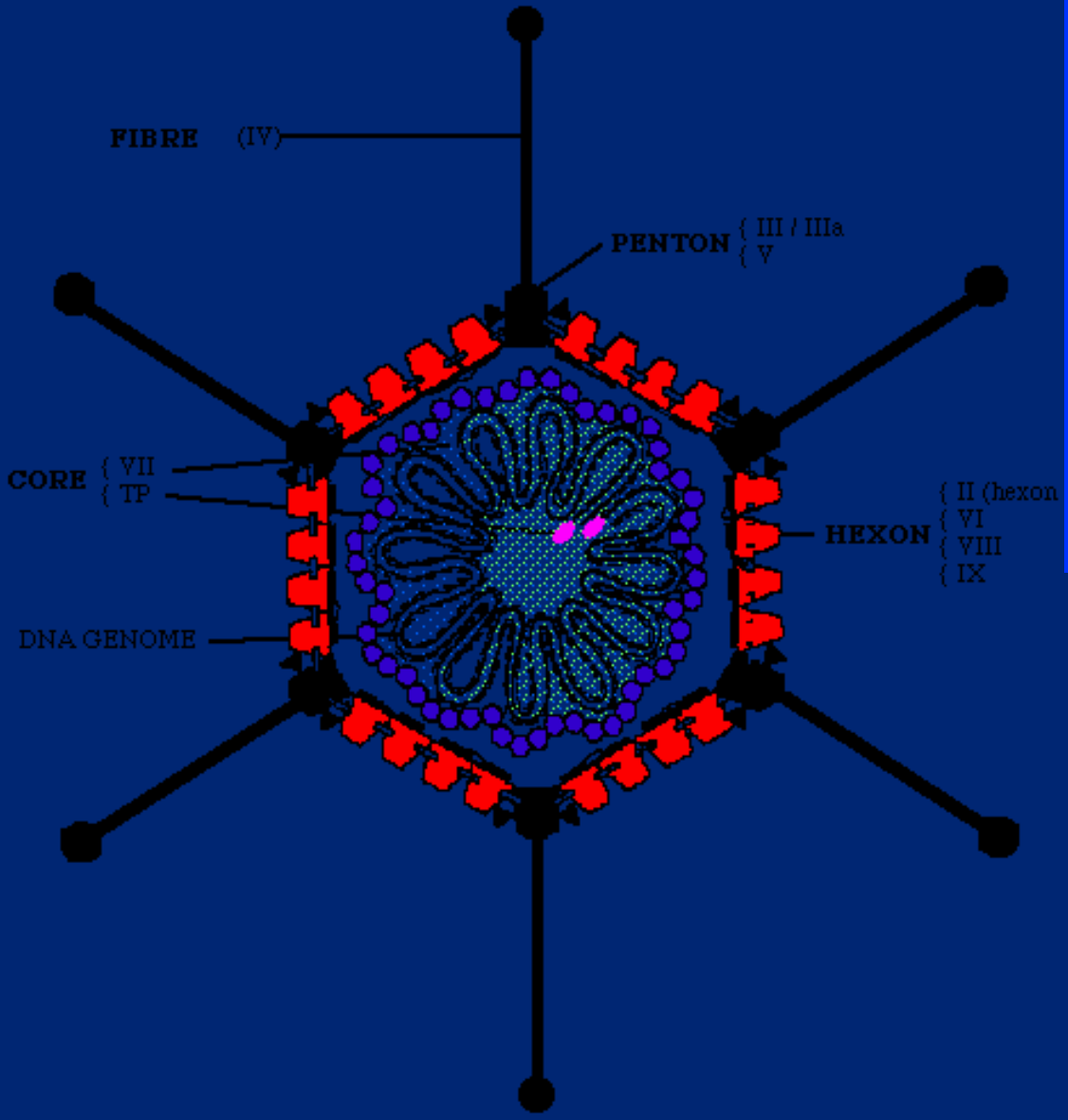
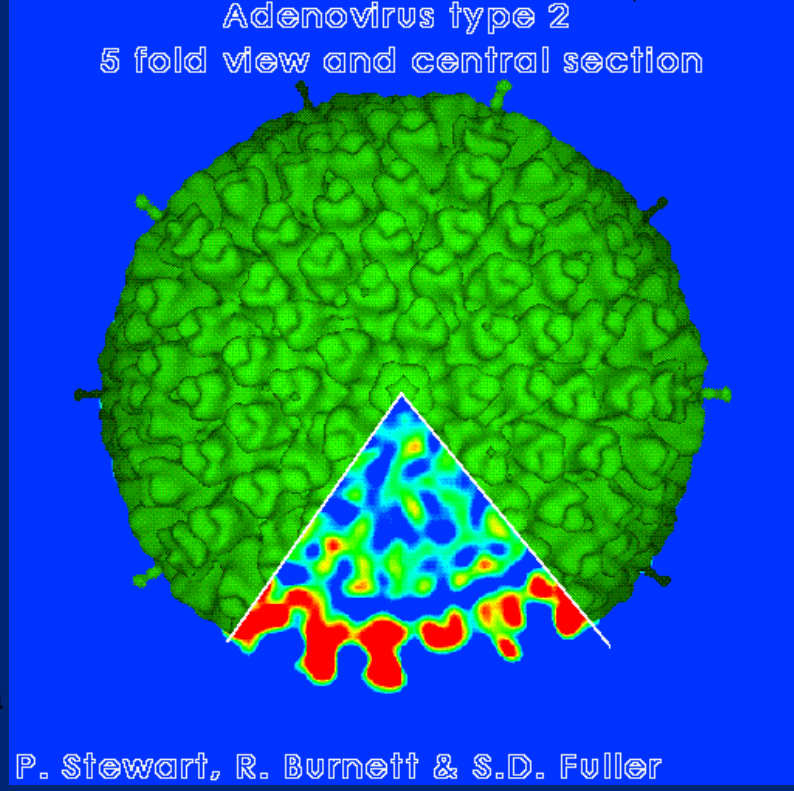




Adenoviruses

Figures are from your text, Flint et al. 2004, ASM Press, unless noted otherwise

Classification

- Group: I (ds DNA virus)
- Family:Adenoviridae
- Genera: 5 genera
  - Genus Mastadenovirus (all human adenovirus)
- Species: 7 HAVA to HAVG
- 57 different serotypes

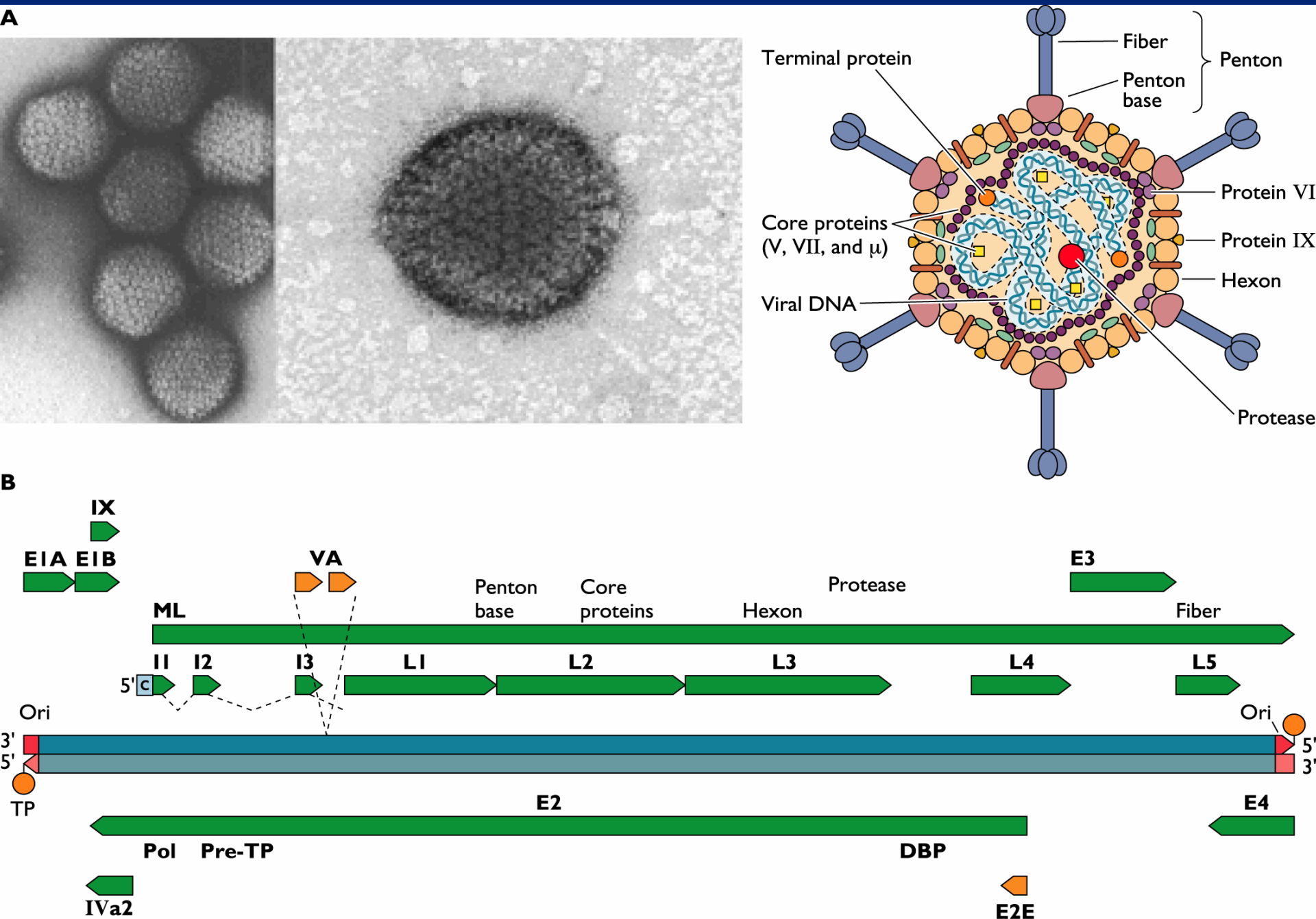
Adenovirus properties

- Nonenveloped icosahedral 65-80nm
- 252 capsomere, 240 hexons and 12 pentons base, fibre with HA activity
- Linear dsDNA 30-38 kbp contains 5'TP
- Encode 25-30 proteins, 15 are structural
- Both strands transcribed in nucleus
- Ordered, timed expression of viral genes
- Virus assembly in nucleus
- Cause respiratory, eye, and intestinal infections
- Some induce tumors in rodents

Adenovirus particle properties

- Structure well characterized
- Nonenveloped icosahedra 65-80nm with prominent spikes
- 3 sets of proteins:
  1. Capsid
     1. 720 hexon polypeptides II
     2. 60 penton base polypeptides III
     3. 60 trimeric polypeptide IV fiber proteins
  2. Scaffolding
     1. 360 monomers of polypeptide VI
     2. 240 monomers of polypeptide IX
     3. IX, IIIa and VI form scaffold that holds capsid together
  3. DNA binding core
     1. Protein V
     2. Protein VII
     3. Terminal protein (TP)
     4. Protease

Adenovirus structure and genome organization www.viralexpasy



Genome map

- Non segmented ds linear DNA 35kb
- Terminal redundant sequence with inverted terminal repeats (ITR)
- Terminal protein 5’ attached covelently
- Genes: Early and late transcription
- Transcribed by host RNA pol II
- Undergo alternative splicing for multiple mRNA

Adenovirus Entry

- Use Integrins receptors (cell adhesion receptors
  - Use CAR receptor (CoxSackie virus and Adenovirus receptor) transmembrane glycoprotein present on epithelial cells
  - Heparin Sulphate
- Adenovirus penton base with RGD peptide

Adenovirus transcription

- 5 early, 1 late transcriptional unit
- Early mRNAs modified by differential splicing (E1-E4)
- Late mRNAs derived from single primary transcript of 29,000 nt that is spliced and differentially polyadenylated to yield at least 18 mRNAs in 5 major families
- First demonstration of mRNA splicing in eukaryotes was with adenovirus model

Adenovirus early gene expression

- Three important functions:
  - Induce host to enter S-phase (E1A, E1B)
    - Active DNA replication phase of cell cycle; causes quiescent cells to become active
    - Products of E1A and E1B transcripts responsible for transformation and oncogenesis
  - Protect virus from host defense (VA RNA)
  - Synthesize replication-associated proteins (E2B)

Host Virus interacting proteins

- E1a drives cells into S phase. Leads to p53 accumulation and apoptosis. To prevent E1B 19K-beclin ,E1b 55K, E4 inhibit apoptotic proteins Bcl-2 and p53
- E19 blocks MHC class I TAP protein
- E1a blocks Interferon induced anti viral activity

Adenovirus infection cycle

1. Entry by endocytosis; release of core
2. Entry of DNA/core protein complex to nucleus

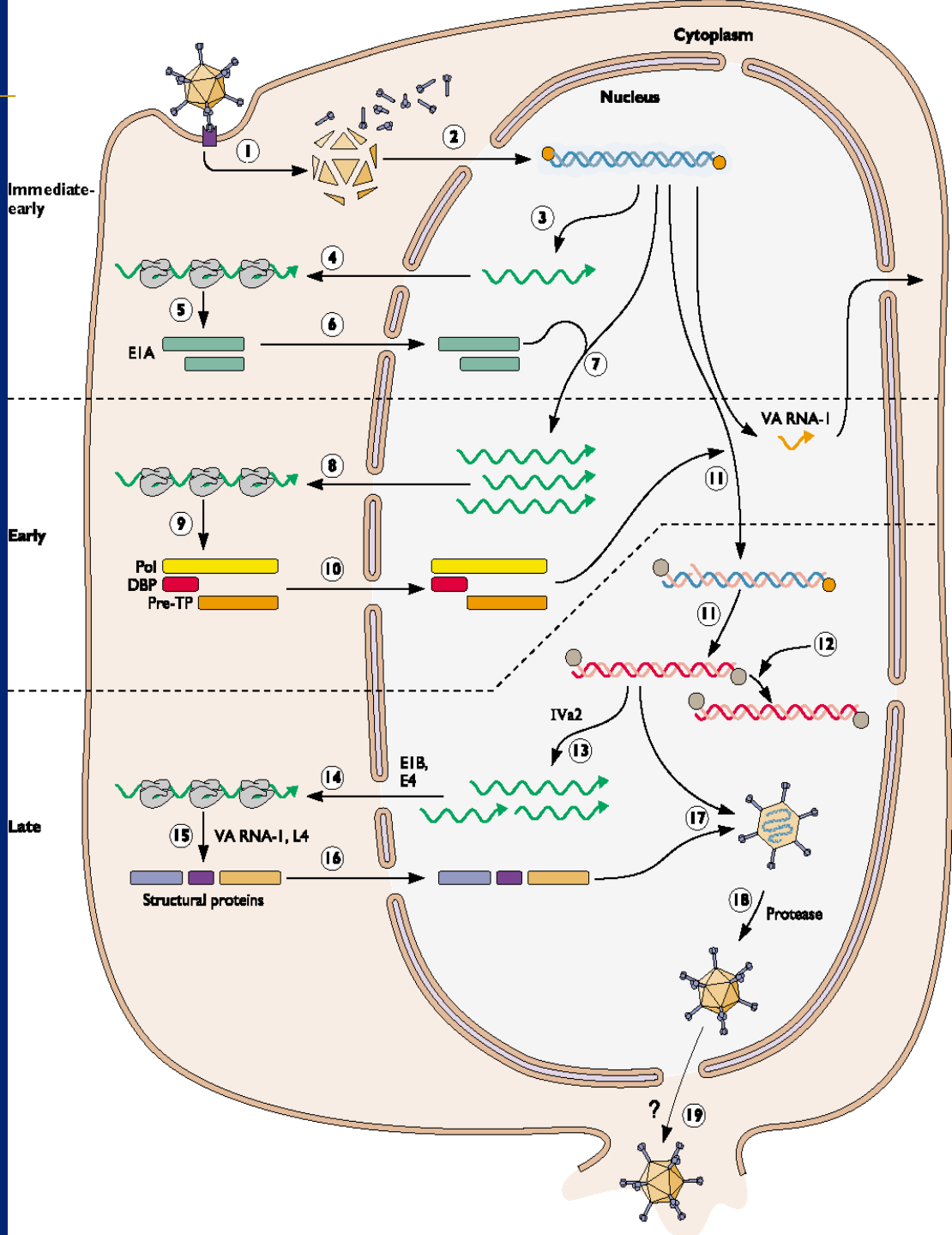
3-5. Synthesis of E1A and E1B transcripts; export to cytoplasm & translation

6-9. Import of E1 proteins into nucleus; transcription, export & translation of Early proteins

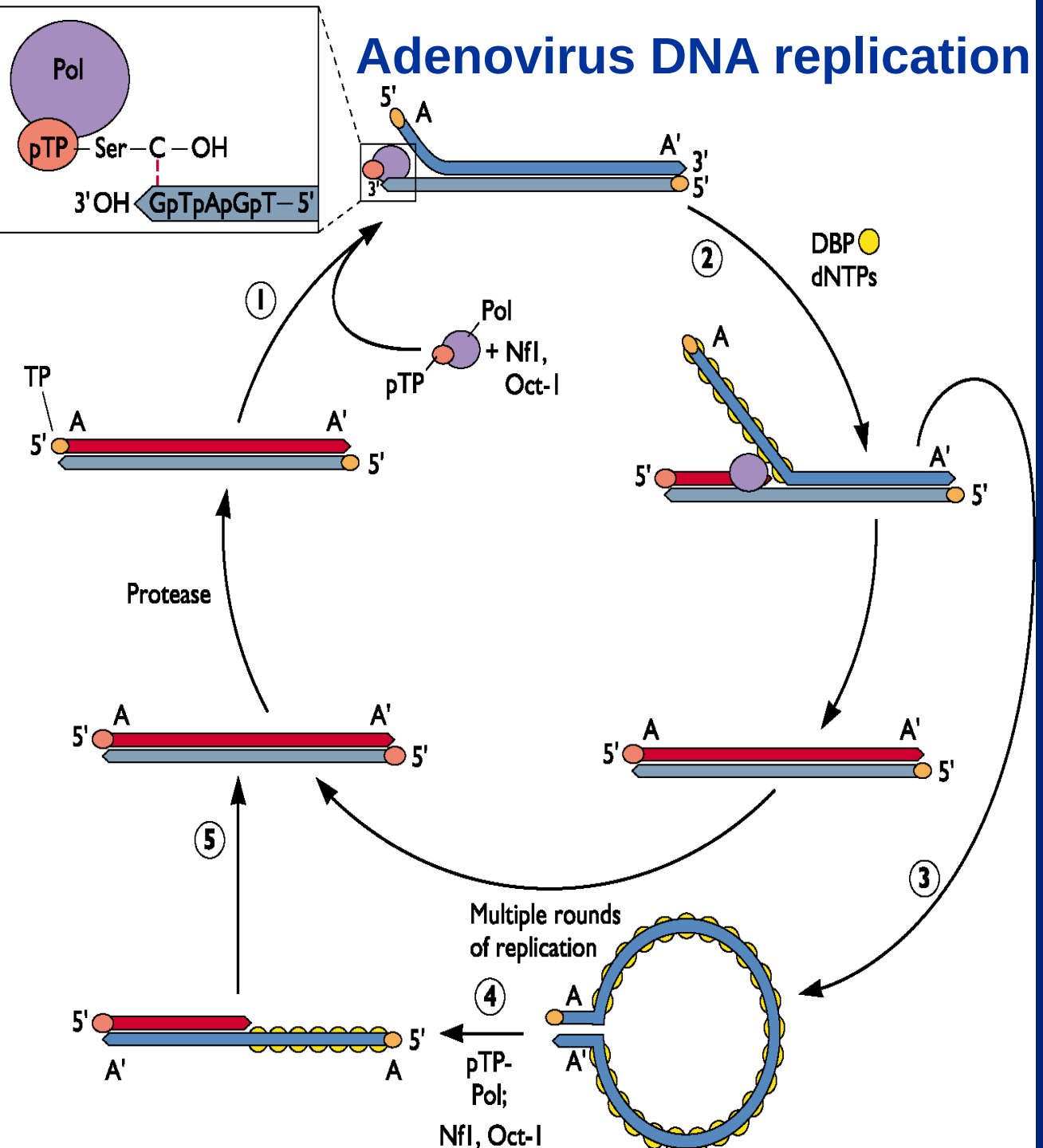
10-13. Early proteins imported to nucleus; combine with host proteins in DNA replication, late gene transcription

14-17. Transcripts exported to cytoplasm, translated to structural proteins, imported to nucleus

18-19. Particle assembly and egress



Adenovirus DNA replication



Adenovirus DNA replication is a protein-primed process that occurs in the nucleus:

1. Preterminal protein (pTP)/DNA polymerase (Pol) complex formed (both E2 proteins)
2. Continuous 5'>3' synthesis of DNA by viral polymerase; DNA coated by ssDNA Binding Protein (DBP)
3. Because of terminal repeats, origin of replication reforms on displaced strand, leading to further replication

Adenovirus associated disease

- Most disease self-limiting, lasts ~ 2 weeks
  - Upper respiratory
  - Lower respiratory
  - Gastrointeritis
  - Conjunctivitis
  - Pharyngitis
  - Endemic in pediatric populations
  - Adenovirus oncogenically transforms rodent cells, but not human cells

Disease depends on strain, patient age, transmission route

Adenovirus transmission

- Ingestion/Fecal-Oral
- Respiration (through droplets)
- Contact/hand to eye

Adenovirus prevention

- Chlorination of pools, drinking water
- Personal hygiene
- Hand washing

Adenovirus pathogenecity

- Enter host and replicate in epithelial cells of URT or enteric organs
- Spread to regional lymph nodes: cervical, adenoids
- In immunocompromised host: spread and cause ARDS (acute respiratory distress syndrome)

- Cause
- (a) lytic infection: mucoepithelial cells of RT, GIT, conjunctiva, cornea damaging cells and spread to visceral organs
- CPE: grape like clusters without cell lysis
- (b) latent infection/persistent infections: young children lymphoid cells are site for latent infection where DNA integrates into host DNA
- © transforming infection: E1 protein

Symptoms

- Acute Pharyngitis: fever, sore throat, atypical pneumonia
  - Complications in infants and geriatrics
- Acute Respiratory Disease (Serotype 4,7,21)
- Adenoviral conjuncitivitis
- Gastroenteritis: diarrhoea

Laboratory Diagnosis

- Virus isolation in cell culture
- DNA hybridization
- PCR
- Electron microscopy
- ELISA
- Agglutination

Treatment

- Ribavirin/Cidofovir (synthetic guanosine analogues) in immunocompromised individuals
- No vaccine, preventive therapy

- Gene therapy using Adenovirus vectors

References

- Flint et al
- Wikipedia- https://en.wikipedia.org/wiki/Viral_replication
- https://en.wikipedia.org/wiki/Adenovirus_genome
- www.viralexpasy.com